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TITLE: SUICIDE INHIBITORS OF REVERSE TRANSCRIPTASE IN THE THERAPY OF AIDS AND OTHER RETROVIRUSES

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Fort Detrick, Frederick, Maryland 21702-5012

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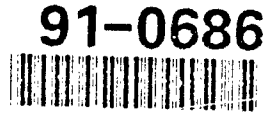

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13. ABSTRACT *(Maximum 200 words)*

The final year of the contract has been quite productive and significant advances have been made in a number of areas.

Groups of compounds were synthesized as potential suicide inhibitors of viral polymerases. Test results from compounds submitted to the U.S. Army antiviral screening program have been received and are summarized below. Full details of active compounds are given in the Appendix to this report. Of the 40 compounds tested to date, significant antiviral activity against one or more of the 11 test viruses have been observed for a surprisingly high proportion. 16 compounds in all have shown some antiviral activity. Several of these have low cytotoxicity and small animal test are planned in collaboration with the Army antiviral screening program if the current (residual) funding proves sufficient.

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INDEX

SUMMARY

1. The final year of the contract has been quite productive and significant advances have been made in a number of areas.

2. Groups of compounds were synthesized as potential suicide inhibitors of viral polymerases. Test results from compounds submitted to the U.S. Army antiviral screening program have been received and are summarized below. Full details of active compounds are given in the Appendix to this report. Of the 40 compounds tested to date, significant antiviral activity against one or more of the 11 test viruses have been observed for a surprisingly high proportion. 16 compounds in all have shown some antiviral activity. Several of these have low cytotoxicity and small animal test are planned in collaboration with the Army antiviral screening program if the current (residual) funding proves sufficient.

3. Cellular components have been identified that produce up to a 1,000-fold increase in the sensitivity of HIV-reverse transcriptase to the pyrophosphate analog phosphonoformate (Foscarnet).

4. The following table summarizes the compounds found to have antiviral activity and the target virus against which they were effective.

Virus	Compounds showing significant antiviral activity (AVS #'s)					
HIV		6460	6457	6455	6466	
Vaccinia		6462	6467			
Punta Toro	6442	6443	6444	6445	6449	6462
Yellow Fever		6456	6458	6444	6445	

Further details for each compound are given in the Appendix Section.

A. INTRODUCTION

The principle that inhibitors of reverse transcriptase will inhibit replication of retroviruses is well established. For example, 3'-azido-3' deoxythymidine, the triphosphate of which inhibits the RT activity of HIV, is a potent inhibitor of virus replication in cultured H-9 cells in the range of 1-10 micromolar and is being used successfully in patients with AIDS. Prolonged administration may cause serious side effects. Another agent which has shown promise is phosphonoformate (PFA, Foscarnet) which inhibits the RT activity of HIV with an I_{50} of only 0.1 micromolar. However, much higher concentrations of up to 340 micromolar are required for complete inhibition of HIV replication in H-9 cells. Other drugs including the dideoxycytidines which are also based upon inhibition of RT by chain termination of the viral template are in clinical trial. Since none of these drugs permanently inactivate the reverse transcriptase and since they do not accumulate intracellularly in significant amounts, virus replication will resume when blood levels of the drugs decrease.

This project represents a collaborative effort between groups of investigators with expertise in virology, cell biology, enzymology, drug design and organic synthesis, to develop new types of antiviral drugs. Novel anti-HIV drugs are being developed based upon the principles of (i) compounds designed to accumulate intracellularly at the sites of viral replication (ii) slow release lipid soluble prodrugs having a long biological half life and capability to accumulate in brain tissues (iii) synergistic combination drugs designed to reduce side effects and development of drug resistance during long-term therapy.

B. WORK ACCOMPLISHED

1. Cellular Pharmacokinetics of Sterol Phosphonoformates.

The first class of compounds are lipid soluble sterol derivatives of the pyrophosphate analog PHOSPHONOFORMIC ACID (PFA). This compound is an excellent in vivo inhibitor of reverse transcriptase with I_{50}'s as low as 0.1 μM for the HIV-RT when transcribing from the viral template. The drug is also relatively non-toxic and acute dosage blood levels of up to 300 μM have been reported without serious side effects. The antiviral potency of the compound however is low with concentrations up to 330 μM being required for complete inhibition of HIV replication in tissue culture. Simple esterification derivatives do not improve the antiviral potency.

The sterol phosphonoformates which we have developed thus represent a significant advance in the pharmacology of antiviral drug delivery to cells. They are replication-site directed inhibitors designed to enter and accumulate in cells via the endocytotic pathway normally used for cholesterol esters. Subsequent hydrolysis by lysosomal sterol esterases results in slow release of PFA at the intracellular sites where the first critical steps in HIV replication take place. Some of the cholesterol phosphonoformate derivatives we have synthesized display a 20-30 fold increase in potency against virus replication in tissue culture, compared to the parent compound PFA.

One of the major goals of this project is the further development of this class of compounds into effective therapeutic agents. These studies will include synthesis and evaluation of ligands which enhance cellular accumulation, those which regulate hydrolysis, and those which enhance anti-viral activity against HIV replication in a standardized tissue culture assay system. A novel and potentially useful therapeutic property which has been observed is the ability of these sterol analogs to accumulate intracellularly and protect cells against virus for up to 8 days following drug removal. The pharmacokinetic studies we are proposing on blood-brain and tissue distribution and half life of these compounds in vivo are designed to investigate their suitability as potential agents for long-term antiviral therapy.

2. Sterol Carboxylate Diesters of AZT, DDC and nucleoside spiroxiranes (NSO):

An extension of this strategy which has proved successful with PFA is being applied to improve the pharmacokinetic properties of AZT, dideoxycytidine (DDC) and nucleoside spiroxiranes. The nucleoside spiroxiranes are a new class of mechanism based (suicide) inhibitors of the reverse transcriptase. These nucleoside analogs are effective inhibitors of reverse transcriptase and viral replication but have very short blood half lives and do not accumulate intracellularly. Virus replication probably recovers soon after blood levels of the drugs fall. Here the problem is not to

increase the cellular permeability of the compounds which is adequate, but to enhance the intracellular accumulation in a slow-release form.

The effect on their pharmacokinetic properties of modifying these compounds by conversion to the 5' sterol dicarboxylates will therefore be investigated. These compounds are designed to incorporate into the lipoprotein and chylomicron particles in the same manner as the long-chain cholesterol esters and phospholipids. Cholesteryl sebacylchloride has been used previously to make synthetic lipoproteins. Sterol and ester hydrolases are present in the lysosomes which will regenerate the active compounds. In pilot studies ^{3}H-AZT cholesteryl sebacylate has been synthesized and uptake by cultured lymphocytes confirmed (see preliminary data section). Appropriate changes in the sterol and linker moieties will be made and the effects on cell accumulation, intracellular release and prolongation of antiviral protection will be evaluated. In addition, the unlabelled AZT-cholesteryl sebacate, succinate and carbonate esters have been synthesized and inhibited viral replication in tissue culture.

3. Development of Synergistic Combination Drugs:

The basic hypothesis underlying this approach is that drug dosages and side effects can be reduced and antiviral potency increased by suitable combinations of drugs directed at different facets of the viral replicative process. In addition, combination drugs lessen the opportunity for drug resistant variants of the virus to appear because of the low probability of simultaneous mutations against two mechanistically different inhibitors. This approach therefore has required basic information on the effects of different drugs on the various steps involved in intracellular replication of the HIV virus, using the purified HIV-RT to obtain detailed information on the kinctic interactions of the HIV reverse transcriptase with potential inhibitors. As an example of the application of this type of information, the nucleotide and template specificity of the RT has been studied with respect to inhibition by PFA. PFA inhibits only the step in viral replication in which TTP is being incorporated into the viral template. Incorporation of dCTP is relatively insensitive to PFA. Furthermore PFA inhibition is not competitive with respect to TTP for the HIV-RT, indicating that mutations that confer AZT resistance are unlikely to result in co-resistance to PFA.

Part of the antiviral potency of AZT in addition to inhibiting RT has been attributed to its ability to inhibit thymidine kinase, thus lowering intracellular TTP levels. These results taken together suggest that additive or synergistic effects should be observed in joint therapy of the sterol phosphonoformates with AZT, DDC or NSO. Since the side effects of these drugs are directed in part at different facets of cell metabolism whereas the antiviral effects are focussed on the viral reverse transcriptase, a combination of drugs at levels insufficient to impair cell metabolism may nevertheless give complete inhibition of virus replication. The successful development of the sterol dicarboxylates of AZT renders this approach particularly attractive, since all three types of inhibitor are now potentially available in slow-release and long acting forms.

4. Expression of HIV-Reverse Transcriptase In Different Cell Lines.

In order to determine if the recombinant HIV-reverse transcriptase was expressed in different forms depending upon the cell type, the vaccinia VCF-21 construct was grown in a number of different cell lines of both human, monkey and rodent origin. The expressed reverse transcriptase was tested for inhibition by Foscarnet at two different levels (1 and 10 nanomolar) and compared to the E. Coli recombinant HIV-RT (Kindly donated by Dr. Steven Hughes Fort Detrick M.D.) and the wild type HIV-RT. Both the wild type and E. Coli HIV-RT's were resistant to PFA showing essentially no inhibition at the 10nM level. Previous studies have shown that both enzymes have I_{50}'s for PFA in the 200-400 nM range. The recombinant HIV-RT expressed in eukaryotic cells however showed a range of phenotypes as indicated in figures 3 and 4 below. Both U-937 and Vero cells expressed enzyme sensitive to 1 nanomolar PFA, whereas human embryo lung and A-498 cells expressed RT-enzyme having wild-type sensitivity. Hela, HuTK- and CV-1 cells as observed previously expressed enzyme having intermediate PFA sensitivity (Figure 1).

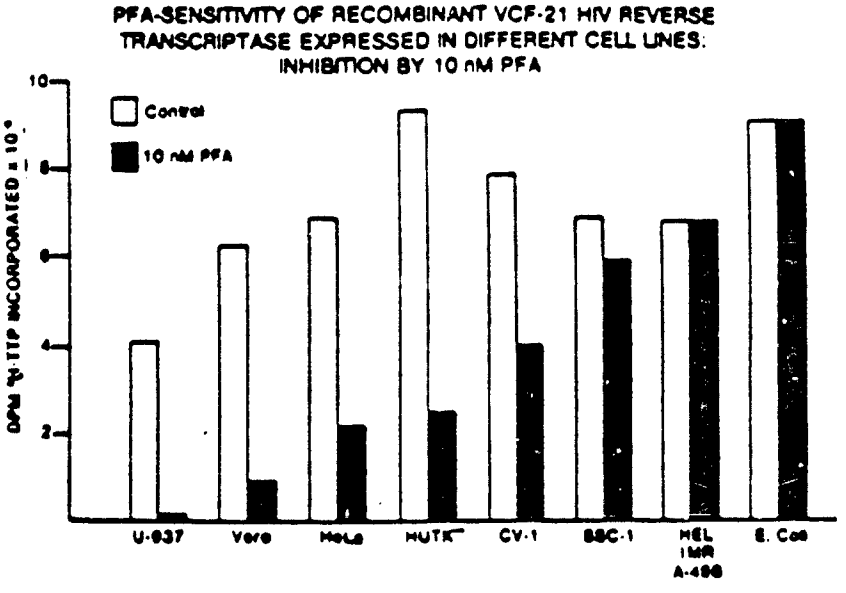


Figure 1: Sensitivity of Recombinant HIV-Reverse Transcriptases to 10 Nanomolar PFA.

The VCF-21 vaccinia construct was grown in the indicated cell lines and the activity of the expressed reverse transcriptase was measured in the presence (dark blocks) or absence (open blocks) of 10 nanomolar PFA.

5. Sentivity of Recombinant HIV-Reverse Transcriptase to Foscarnet.

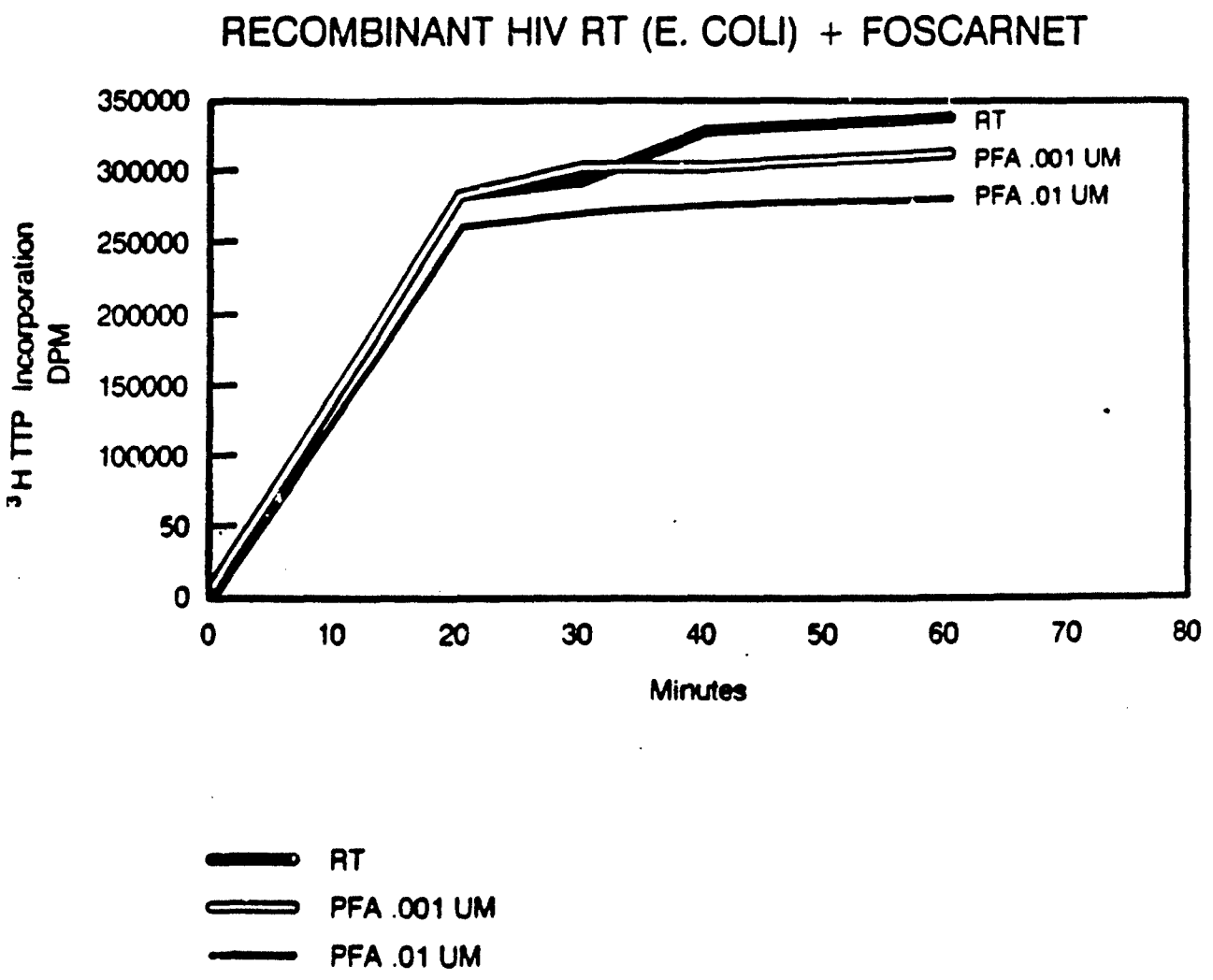


Figure 2. Activity of a recombinant (E. Coli produced) HIV-RT was assayed using ^{3}H-dTTP and poly rAdT$_{10}$template both without inhibitor PFA and in the presence of 0.001 μM and 0.01 μM PFA. Note the relative insensitivity of the enzyme to these low concentrations. The I_{50} of the E. Coli recombinant HIV-RT for PFA was shown to be 0.4 μM which is similar to that of the wild type HIV-RT.

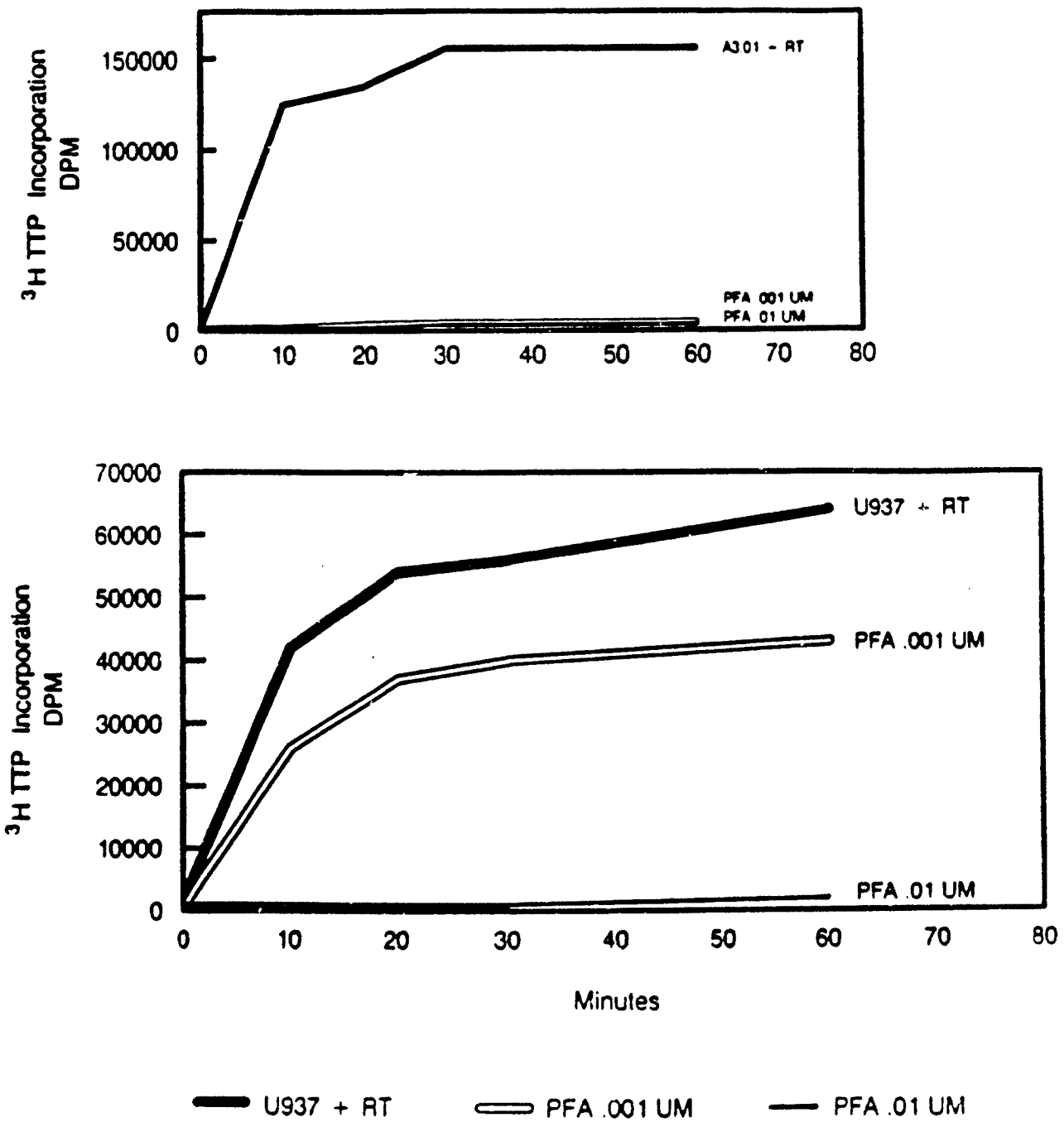


Figure 3. The E. Coli recombinant HIV-RT was incubated with PFA under the same conditions as Figure 1R, with the addition of lysates from A.301 cells (upper panel) or U937 cells (bottom panel). Note that the lysates markedly increase the sensitivity of the reverse transcriptase to inhibition by PFA.

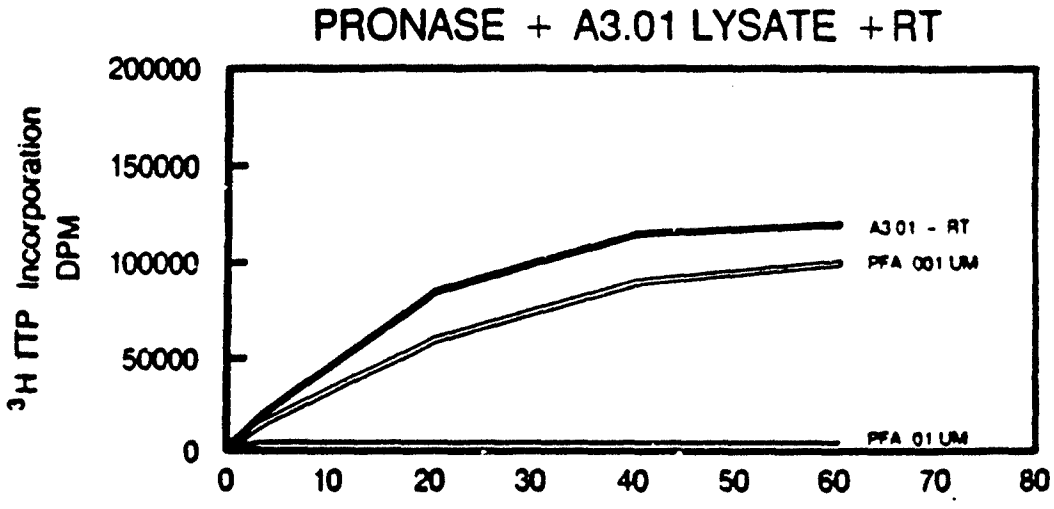


Figure 4. The E. Coli recombinant HIV-RT was incubated with PFA and cell lysates under the same conditions as in Figure 2R with the exception that the lysates were preincubated with pronase for 30 minutes and heat inactivated. Note that neither treatment destroyed the PFA sensitizing activity of the cell extracts.

SENSITIVITY TO FOSCARNET INHIBITION OF HIV REVERSE TRANSCRIPTASE (PURIFIED) IN THE PRESENCE OF CELL LYSATES

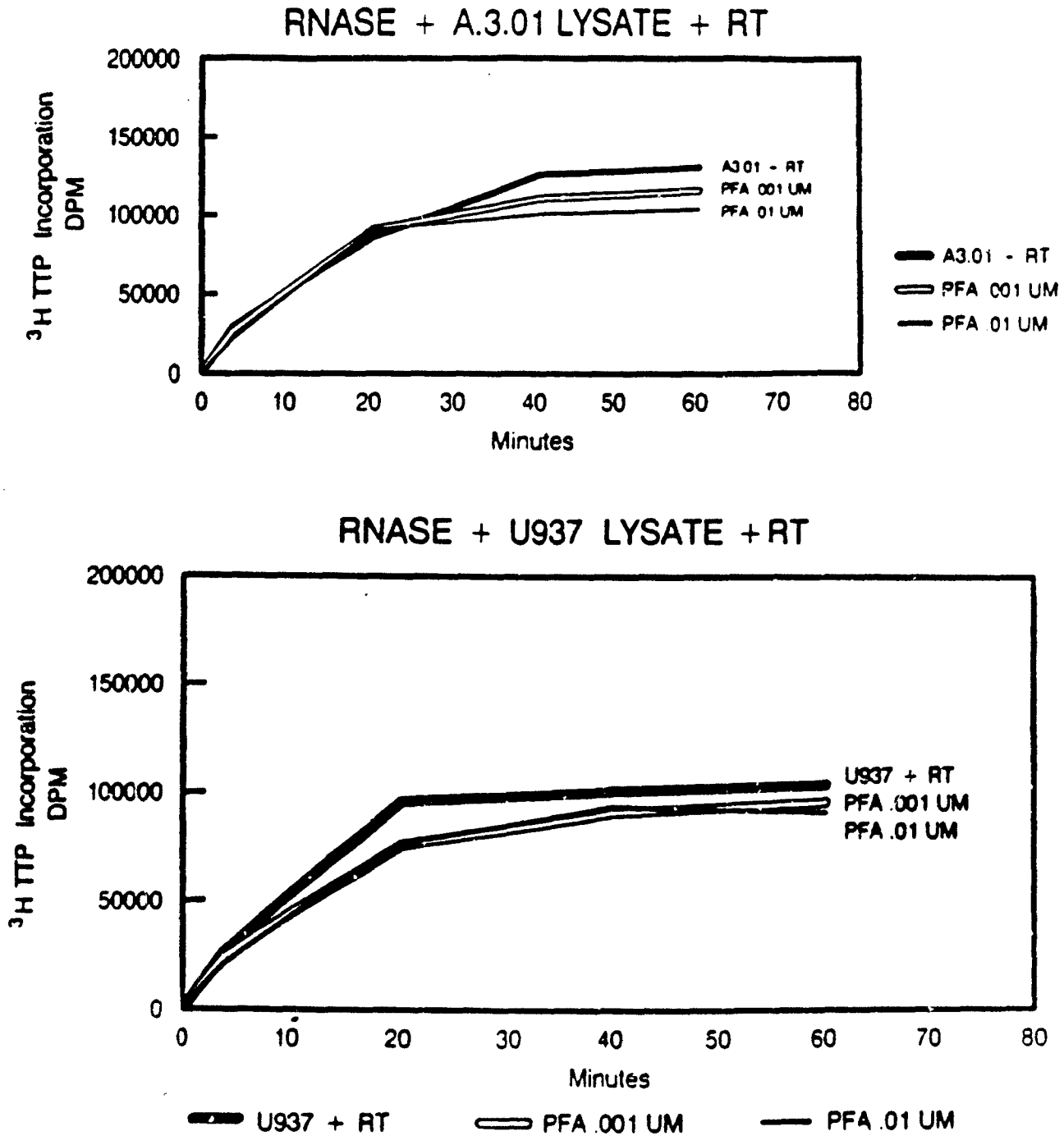


Figure 5. The E. Coli recombinant HIV-RT was incubated with PFA and cell lysates under the same conditions as Figure 2R with the exception that the lysates were preincubated with pancreatic ribonuclease for 30 minutes. Note that the RNAse treatment completely destroyed the PFA sensitizing activity of the extracts.

Since the molecular weight of the sensitized, purified recombinant RT prepared from sensitizing cell lines was not substantially different from that of wild type enzyme, these observations suggest that the sensitizing activity may be associated with a copurifying RNAse sensitive material of relatively low molecular weight.

6. Drug Screening Results.

Test results from 26 of the compounds submitted to the U.S. Army antiviral testing facility have been received. A number of compounds were identified that have activity against one or more of the 11 viruses in the test battery. Of these 4 were active against HIV (Appendix III), and 9 were active against Vaccinia, Punta Toro and Yellow Fever viruses (Appendix IV).

Several of these compounds have very favorable therapeutic indices and have been selected for further testing and development to the limit of currently available funding.

Appendix I.

PUBLICATIONS

PROJECT: DAMD 17-87-C-7171

TITLE: SUICIDE INHIBITOR OF REVERSE TRANSCRIPTASE IN THERAPY OF AIDS AND OTHER RETROVIRUSES.

PRINCIPAL INVESTIGATOR: Dr. J.M. Bailey, Ph.D., D.Sc.
Professor of Biochemistry

PRODUCTIVITY REPORT

Publications:

1. Enhanced sensitivity to Foscarnet of first-strand viral replication by recombinant HIV-reverse transcriptase. M.M. Lightfoote and J.M. Bailey. *FASEB J.* 4:1318 (1990).

2. Differential sensitivity of wild-type and recombinant HIV-Reverse transcriptase to inhibition by Foscarnet. M.M. Lightfoote and J.M. Bailey. *Proc V^th Int. AIDS conf. Montreal* 5:515 (1989).

3. M.M. Lightfoote and J.M. Bailey. Somatic Cell Modulation of HIV-Reverse Transcriptase Expression. *Antiviral Chem. and Chemotherapy.* (1989) in preparation.

4. Nucleotide and template selectivity for inhibition of reverse transcriptase by PFA: Implications for retroviral therapy. J.M. Bailey and M.M. Lightfoote. *Proc. IV^th Int. AIDS Conf. Montreal.* 4:3223 (1988).

5. Differential sensitivity of wiid-type and recombinant HIV-reverse transcriptase to inhibition by foscarnet. M.M. Lightfoote and J.M. Bailey. *Proc. IV^th Int. AIDS Conf. Montreal.* (1989).

6. Antiviral activities of some sterol phosphonoformate diester. J.M. Bailey, K. Nelson, M. Lightfoote. *J. Clin. Exp. Ther.* in preparation.

7. Nucleoside spiroxiranes: A new class of retroviral inhibitor. J.M. Bailey, K. Nelson, M. Lightfoote. *J. Virol.* in preparation.

8. Synthesis and antiviral activities of some sterol dicarboxylate esters of 3'Azido thymidine (AZT). J.M. Bailey, R.M. Mook, M. Lightfoote. *J. Clin. Exp. Ther.* in preparation.

9. Synthesis of mono and di-substituted cholesterol phosphonoformates by the Arbuzov reaction. J.M. Bailey and Keith Nelson. *Tetrahedron Letters.* in preparation.

Appendix II

COMPOUNDS SYNTHESIZED:

Compounds synthesized and prepared for shipment to USAMRIID for antiviral testing.

1. 2',0^2-Anhydrouridine
2. 2',0^2-Anhydrocytidine hydrochloride
3. 3',5'-Di-0-benzoyl-2'-0^2-anhydrouridine
4. 5'-0-t-Butyldimethylsilyl-3'-0-benzoyl-2',0'-anhydrouridine
5. 2',3'-Anhydro-5'-0-trityluridine
6. 3'-Deoxy-2'-thymidinene
7. N^3-Benzyl-2',5'-di-0-trityluridine
8. 5'-0-t-Butyldimethylsilylanhydrouridine
9. N^4-Benzoyleytidine
10. 2',3'-Di-0 -mesyl-5'-0-trityluridine
11. 5'-0 -t-Butyldimethylsilyl-2',3'-isopropylideneuridine
12. 2',3'-Isopropylideneuridine
13. 2',3'-0-Sulfinylurid' ?
14. 2',3'-Benzylideneuridine
15. N^4-Benzoyl-2',3'-0-Sulfinylcytidine
16. 2',3'-0-Sulfinylcytidine
17. 3',5'-Di-0-trityl-2'deoxy-2'-oxouridine
18. 3',5'-Di-0-t-butyldimethylsilyl-2'-deoxy-2'-oxouridine
19. 2',5'-Di-0-t-butyldimethylsilyl-3'-deoxy-3'-oxouridine
20. Diethyl (cholesteryloxycarbonyl) phosphonate
21. Disodium (cholesteryloxycarbonyl) phosphonate
22. Di-[1-(3-carboethoxypropyl)] cholesteryloxycarbonyl
23. Di-(2,3-isopropylideneglyceryl) cholesteryloxycarbonyl phosphonate
24. Di-[1-(3-methylbutyl)] cholesteryloxycarbonyl phosphonate
    Di-[1-(lithium 3-carboxypropyl)] cholesteryloxycarbonyl phosphonate
25. Sodium ethyl (cholesteryloxycarbonyl) phosphonate

26. Sodium 1-(3-carboxypropyl) 1-(30 carboethoxypropyl) [cholesteryloxycarbonyl] phosphonate

27. Adenosine 2',3'-Riboepoxide

28. Thymidine 5'-(1,3,2-dioxaphosphorin-2-oxide)

29. Thymidinene 5'-(1,3,2-dioxaphosphorin-2-oxide)

30. Thymidinene

31. 2-Ethoxy-5-chloro-6-methyl-1,3,2-dioxaphosphorin-5-ene-2-oxide

32. 2-Ethoxy-5-chloro-1,2-oxaphosphol-4-ene-2-oxide

33. 2,4-dichloro-5-methyl-1,3,2-dioxaphosphole-2-oxide

34. 2-methoxy-4,5-dimethyl-1,3,2-dioxaphole-2-oxide

35. Thymidine 3',5'-oxetane

Appendix III

TEST DATA ON ANTI HIV DRUGS

DEPARTMENT OF THE ARMY
U.S. ARMY MEDICAL RESEARCH INSTITUTE OF INFECTIOUS DISEASES
FORT DETRICK, FREDERICK, MARYLAND 21701-5011

May 10, 1990

REPLY TO
ATTENTION OF:

Department of Antiviral Studies

Dr. J. Martyn Bailey
Professor of Biochemistry and Molecular Biology
The George Washington University
Department of Biochemistry
2300 Eye Street, NW
Washington, DC 20037

Dear Dr. Bailey:

Enclosed please find results of the antiviral activity screening on the U.S. Army's Antiviral Drug Development Program. The enclosed data summarizes the *in vitro* results of the screening done to date.

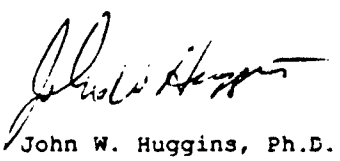
- Older assay methodologies have been reviewed in relation to current program status and predictability. As a result of this review, current data sheets may reflect new data as well as the removal of previously reported data now thought to be supplanted by new assay techniques.

- Data have not been previously reported for compounds showing antiviral activity prior to confirmation. I feel this procedure has unnecessarily slowed the reporting of data to suppliers; hence, we will now report data as it is received. **Please do not make corporate or business decisions based on a preliminary, unconfirmed result without discussing this data with the undersigned or a designated member of the Virology Division.**

Our intent with these changes is to decrease the length of time required to get data to you for review. Please let me know if the new approach to reporting is improved, and if additional modifications might further enhance collaboration.

Correspondence regarding the evaluation of your compounds or the interpretation of screening results should be addressed to the undersigned at U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, Maryland 21701-5011, (301) 663-7494, FAX (301) 698-0854. Alternatively, you may contact Dr. Edward L. Stephen, P.O. Box 248, Monrovia, Maryland 21770, (301) 874-5533.

Sincerely,



John W. Huggins, Ph.D.
Department of Antiviral Studies
Virology Division

Enclosures

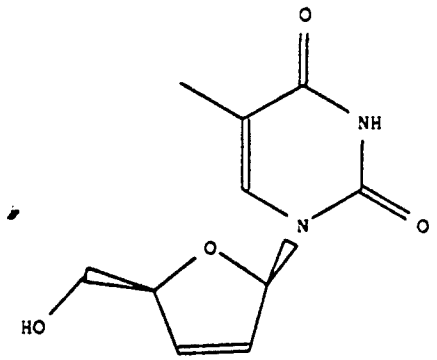
CF: Edward L. Stephen, D.V.M.
Antiviral Information, Compound
Solicitation and Repository

USAMRIID

Antiviral Drug Screening Program

08/06/90

STRUCTURE CHIRAL



SUBMITTER	CTR NO	AVS NO
01141.01	KN-II-55	AVS-006466
DATE RECD	**AMT RECEIVED [mg]**	**MOL WT (au)**
12-28-89	53.30	224.213

HANDLING/STORAGE

SOLUBILITY

STABILITY

ALT NAME

2',3'-DIDEOXYTHYMIDINENE

COMPOUND NAME

2',3'-DIDEOXYTHYMIDINENE

SCREEN INSTRUCTION

PRIORITY=PT>VEE>YF>KHF>PIC>JE>SF>VV>AD2>VSV

IN VIVO TOXICITY [mg/kg]

HOST	VH	RTE	LD50	MTC	LAB PR	DATE

IN VITRO SCREEN [ug/ml]

VIR	VR	VR+	ID50	CELL	MTC	TI	TI+	LAB PRT DATE
HIV			4.99	MT2	66.4	13.29		SO MTT04-APR-90
HIV			.32	CEM	71.1	> 222.13		SO MTT26-APR-90
JE			NOT ACT	VERO	184	0		SO MTT06-MAR-90
PT			NOT ACT	VERO	182	0		SO MTT06-MAR-90
SF			NOT ACT	VERO	171	0		SO MTT06-MAR-90
VEE			NOT ACT	VERO	> 320	0		SO MTT09-MAR-90
YF			NOT ACT	VERO	173	0		SO MTT06-MAR-90

IN VIVO SCREEN [Dose = mg/kg]

VIR	HST	VR	VR+	DOSE	MTC	VEH	RTE	D	TOX	SF	LAB PR	DATE

PLATE 1Q9
DRUG 6460

IN VITRO ANTIVIRAL RESULTS
MTT ASSAY

DRUG: AVS 6460
TAI: >30.24 SI: 2.79

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						plasma background					
A	0.302	0.273	0.281	0.414	0.402	0.296	0.079	0.081	0.259	0.252	0.130	0.071
		cells					tox	drug 6460 experimental			cells	tox
B		1.940					1.999	0.798	0.734	0.680	2.096	2.160
C		1.881					1.993	0.697	0.802	0.720	1.992	1.693
D		1.776					1.987	0.947	0.994	0.879	1.856	1.943
E		0.557					2.067	1.159	0.949	0.911	0.423	2.060
F		0.423					2.018	0.930	1.338	1.309	0.365	1.921
G		0.478					1.223	0.719	0.614	0.637	0.500	0.881
							drug 6460 colorimetric background					
H							0.354	0.270	0.282	0.268	0.273	0.313

tox=cell toxicity cells=cell control vc=virus control BOLD = highest drug conc values shown are optical densities

VIRUS	HIVCRF		
CELLS	CEM	Satisfactory; Active; Retest	
SHIPMENT NUMBER	63		
STRN	RF2		
REAGENT	0.328		
VIRUS CONTROL	0.130		
CELL CONTROL	1.596		
DIFFERENTIAL	1.466		

PROJECT #	6520-2			
SPONSOR	USAMRIID			
TEST DATE	06/12/90			
DATE READ	06/19/90			

DRUG 6460	25%	50%	95%
TC (uG/mL)	82.48	82.28	> 100.00
IC (uG/mL)	1.18	22.40	------
ANTIVIRAL INDEX (AI)	52.61	4.14	------

DRUG 6460		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		
ROW ON PLATE	CONC. (uG/mL)	MEAN O.D.	% RED. IN CPE	MEAN O.D.	% CELL VIABILITY	COLORIMETRIC CONTROL
low B	0.32	0.295	20%	1.767	100%	-.015
C	1	0.337	23%	1.570	98%	-.055
D	3.2	0.542	37%	1.697	100%	-.060
E	10	0.595	41%	1.782	100%	-.046
F	32	0.793	54%	1.700	100%	-.058
high G *	100	0.173	12%	0.698	44%	0.026

* highest drug concentration tested values shown are final adjusted numbers

SUMMARY GRAPH

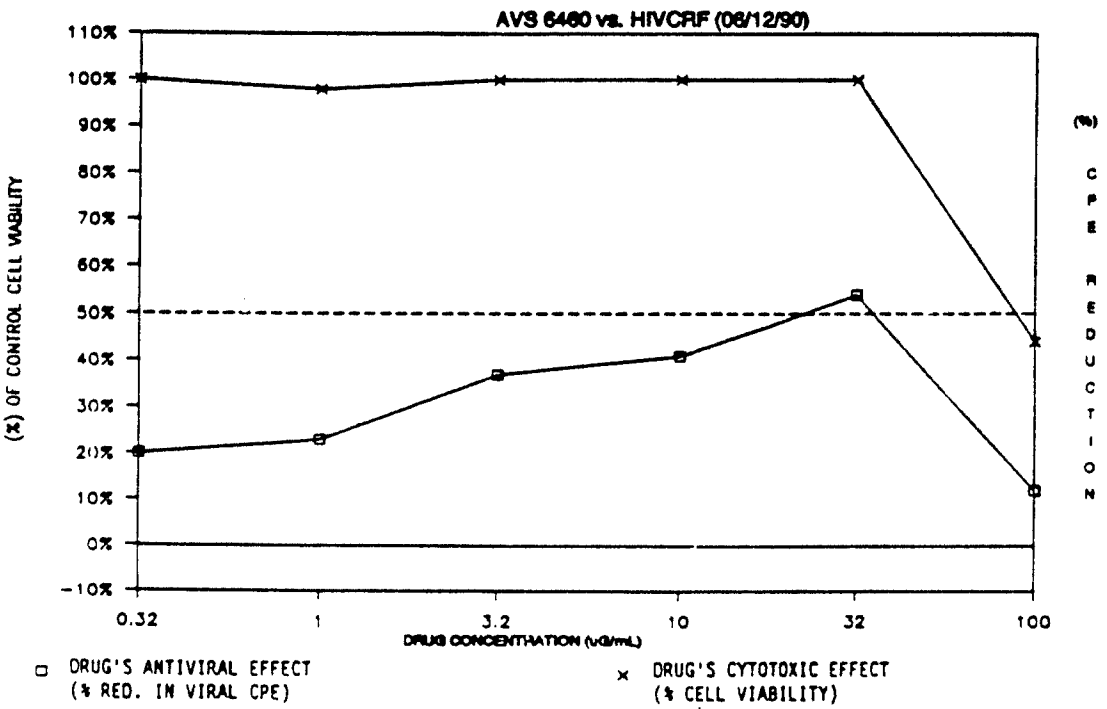


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PLATE 1Q8
DRUG 6457

IN VITRO ANTIVIRAL RESULTS
MTT ASSAY

DRUG: AVS 6457
TAI: >27.78 SI: >1.29

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						plastic background					
A	0.433	0.373	0.552	0.655	0.447	0.451	0.103	0.100	0.191	0.442	0.104	0.087
	tox	cells	drug 6457 experimental			tox					cells	
B	1.739	1.747	0.707	0.601	0.807	1.972					1.841	
C	1.606	1.765	0.674	0.715	1.069	1.794					1.750	
D	1.871	1.913	0.555	0.799	1.037	1.806					2.012	
E	1.782	0.522	0.965	0.990	0.742	1.916					0.811	
F	1.783	0.541	0.894	0.662	1.126	1.899					0.583	
G	1.691	0.602	1.069	1.161	1.241	1.811					0.652	
	drug 6457 colorimetric background											
H	0.345	0.405	0.387	0.396	0.393	0.382						

tox=cell toxicity cells=cell control virus=virus control BOLD = highest drug conc values shown are optical densities

VIRUS	HIVCRF		PROJECT # 6520-2
CELLS	CEM	Satisfactory; Active; Retest	SPONSOR USAMRIID
SHIPMENT NUMBER	63		TEST DATE 06/12/90
STRN	RF2		DATE READ 06/19/90
REAGENT	0.485		
VIRUS CONTROL	0.133		
CELL CONTROL	1.353		
DIFFERENTIAL	1.220		

DRUG 6457	25%	50%	95%
TC (uG/mL)	> 100.00	> 100.00	> 100.00
IC (uG/mL)	4.68	77.80	------
ANTIVIRAL INDEX (AI)	> 21.37	> 1.29	------

DRUG 6457		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		
ROW ON PLATE	CONC. (uG/mL)	MEAN O.D.	% RED. IN VIRAL CPE	MEAN O.D.	% CELL VIABILITY	COLORIMETRIC CONTROL
low B	0.32	0.190	16%	1.473	100%	-.103
C	1	0.293	24%	1.307	97%	-.092
D	3.2	0.269	22%	1.442	100%	-.089
E	10	0.379	31%	1.462	100%	-.098
F	32	0.356	29%	1.436	100%	-.080
high G *	100	0.679	56%	1.406	100%	-.140

* highest drug concentration tested values shown are final adjusted numbers

SUMMARY GRAPH

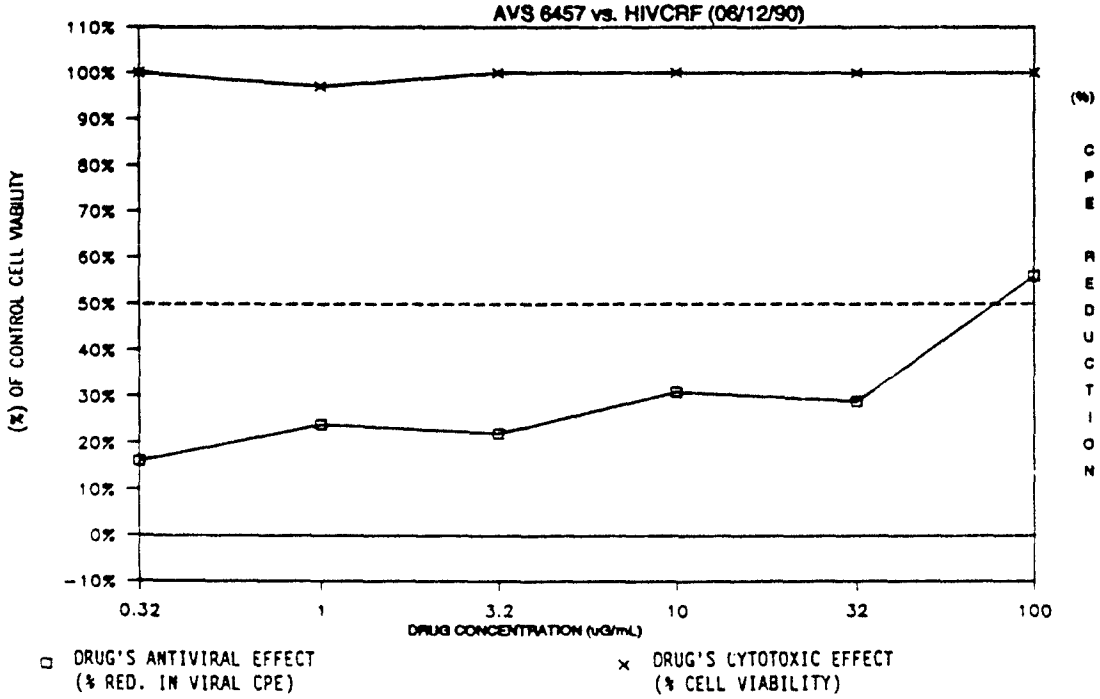

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PLATE 1Q7
DRUG 6455

IN VITRO ANTIVIRAL RESULTS
MTT ASSAY

DRUG: AVS 6455
TAI: >38.98 SI: >5.71

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background								plasma background			
A	0.463	0.349	0.539	0.566	0.386	0.388	0.253	0.256	0.399	0.448	0.239	0.199
	blk	calve	drug 6455 experimental			calc					calve	
B	1.916	1.590	0.861	0.677	0.813	1.889					1.783	
C	1.340	1.486	0.820	0.986	0.873	2.017					1.588	
D	1.800	2.193	0.764	0.557	0.841	1.849					1.641	
E	2.057	0.462	0.856	0.811	1.334	2.016					0.539	
F	1.959	0.636	0.944	1.071	1.242	1.830					0.548	
G	2.003	0.374	1.269	1.478	1.180	1.913					0.607	
	drug 6455 colorimetric background											
H	0.328	0.243	0.480	0.459	0.455	0.448						

blk=cell toxicity calc=cell control calv=virus control BOLD = highest drug conc values shown are optical densities

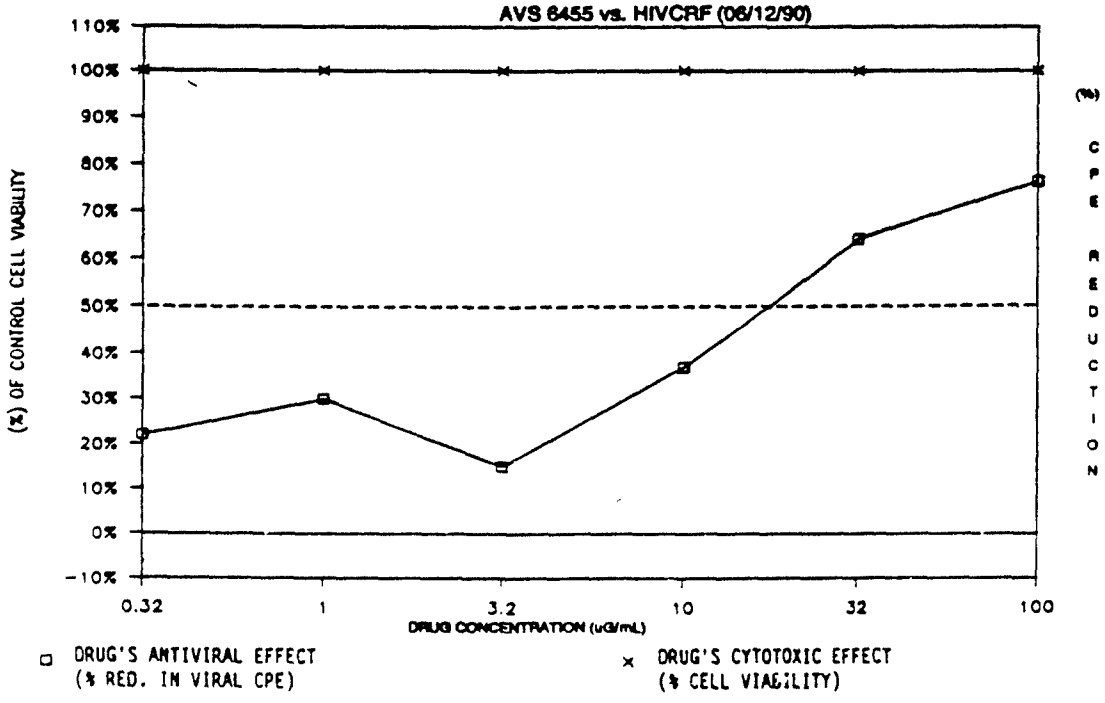
VIRUS	HIVCRF		PROJECT # 6520-2
CELLS	CEM	Satisfactory; Active; Retest	SPONSOR USAMRIID
SHIPMENT NUMBER	63		TEST DATE 06/12/90
STRN	RF2		DATE READ 06/19/90
REAGENT	0.449		
VIRUS CONTROL	0.079		
CELL CONTROL	1.265		
DIFFERENTIAL	1.186		

DRUG 6455	25%	50%	95%
TC (uG/mL)	> 100.00	> 100.00	> 100.00
IC (uG/mL)	0.49	17.50	------
ANTIVIRAL INDEX (AI)	> 203.84	> 5.71	------

DRUG 6455		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		
ROW ON PLATE	CONC. (uG/mL)	MEAN O.D.	% RED. IN VIRAL CPE	MEAN O.D.	% CELL VIABILITY	COLORIMETRIC CONTROL
low B	0.32	0.256	22%	1.454	100%	0.000
C	1	0.358	30%	1.473	100%	0.007
D	3.2	0.182	15%	1.365	100%	0.011
E	10	0.442	37%	1.557	100%	0.031
F	32	0.764	64%	1.652	100%	-.206
high G *	100	0.902	76%	1.631	100%	-.120

* highest drug concentration tested values shown are final adjusted numbers

SUMMARY GRAPH



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Appendix IV

TEST DATA AGAINST OTHER VIRUSES

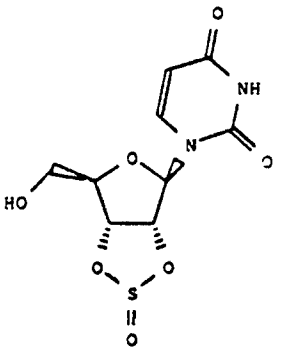
USAMRIID

Antiviral Drug Screening Program

03/26/90

STRUCTURE

CHIRAL



SUBMITTER	CTR NO	AVS NO
01141.01	KN-V-99	AVS-006442
DATE RECD	**AMT RECEIVED (mg)**	**MOL WT (au)**
12-28-89	74.00	290.253

HANDLING/STORAGE

SOLUBILITY

STABILITY

ALT NAME

2',3'-O-SULFINYL URIDINE

COMPOUND NAME

2',3'-O-SULFINYL URIDINE

SCREEN INSTRUCTION

PRIORITY-PT>VEE>YF>KHF>PIC>JE>SF>VV>AD2>VSV

IN VIVO TOXICITY (mg/kg)

HOST	VM	RTE	LD50	MTC	LAB PT	DATE

IN VITRO SCREEN (ug/ml)

R	VR	VR•	ID50	CELL	MTC	TI	TI•	LAB PRT	DATE
			NOT ACT	VERO	183	0		SO MTT	90-03-01
			100	VERO	170	2.39		SO MTT	90-03-01
			NOT ACT	VERO	172	0		SO MTT	90-03-01
E			NOT ACT	VERO	38.3	0		SO MTT	90-03-02
			NOT ACT	VERO	171	0		SO MTT	90-03-01

IN VIVO SCREEN (Dose = mg/kg)

VIR	HST	VR	VR•	DOSE	MTC	VEH	RTE	D TOX	SP L	TR	DATE

PLATE U9A
DRUG 6442

IN VITRO ANTIVIRAL RESULTS
MTT ASSAY

DRUG: AVS 6442
TAI: 15.38 SI: 1.70

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						plate background					
A	0.042	0.041	0.040	0.042	0.039	0.042	0.001	0.001	0.001	0.001	0.001	0.001
	tox	cells	drug 6442 experimental			tox					cells	
B	0.898	0.951	0.392	0.299	0.337	0.956					0.746	
C	0.938	1.033	0.389	0.295	0.345	0.912					0.972	
D	1.011	1.139	0.419	0.423	0.434	1.020					0.800	
E	1.034	0.329	0.559	0.504	0.542	1.102					0.334	
F	1.115	0.389	0.663	0.626	0.656	1.181					0.342	
G	0.263	0.253	0.227	0.227	0.219	0.229					0.396	
	drug 6442 colorimetric background											
H	0.049	0.038	0.038	0.037	0.038	0.039						

tox=cell toxicity cells=cell control virus=virus control BOLD = highest drug conc values shown are optical densities

VIRUS	PT		PROJECT # 5975-1
CELLS	VERO	Satisfactory; Active; Retest	SPONSOR USAMRIID
SHIPMENT NUMBER	63		TEST DATE 03/01/90
STRN	ADAMS5		DATE READ 03/09/90
REAGENT	0.041		
VIRUS CONTROL	0.316		
CELL CONTROL	0.899		
DIFFERENTIAL	0.583		

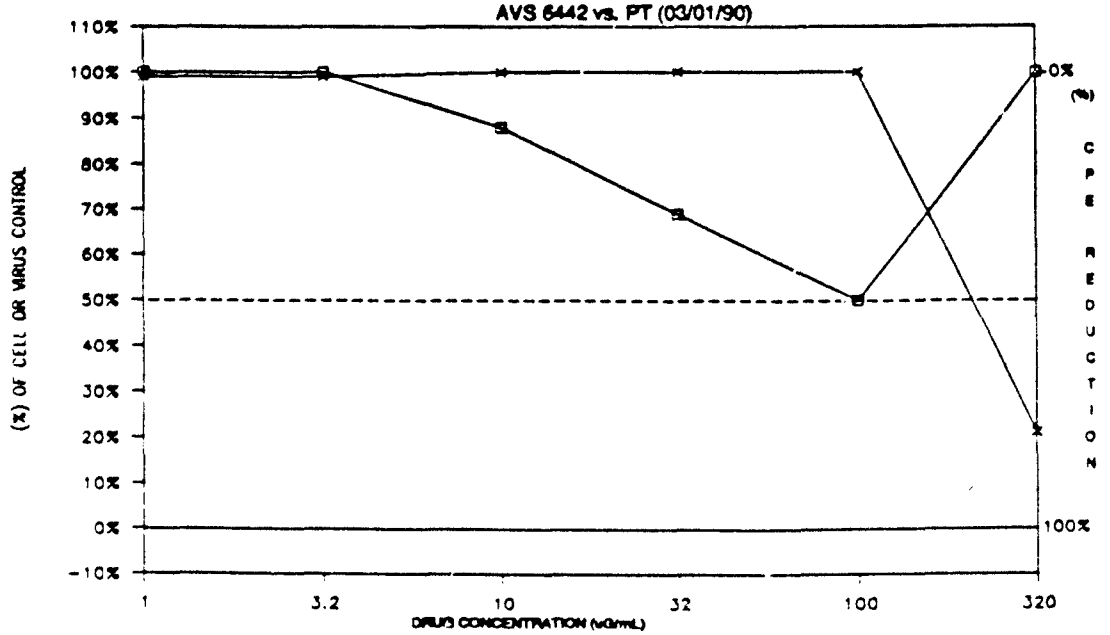
DRUG 6442	25%	50%	95%
TC (uG/mL)	170.00	239.00	> 320.00
IC (uG/mL)	22.20	100.00	------
ANTIVIRAL INDEX (AI)	7.65	2.39	------

DRUG 6442		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		
ROW ON PLATE	CONC. (uG/mL)	MEAN O.D.	% VIRAL CPE	MEAN O.D.	% CELL VIABILITY	COLORIMETRIC CONTROL
low B	1	-.013	100%	0.888	99%	-.002
C	3.2	-.011	100%	0.887	99%	-.003
D	10	0.072	88%	0.979	100%	-.004
E	32	0.161	69%	1.030	100%	-.003
F	100	0.294	50%	1.110	100%	-.003
high G *	320	-.141	100%	0.187	21%	0.008

* highest drug concentration tested values shown are final adjusted numbers

SUMMARY GRAPH

AVS 6442 vs. PT (03/01/90)



□ DRUG'S ANTIVIRAL EFFECT (% VIRAL CPE)

× DRUG'S CYTOTOXIC EFFECT (% CELL VIABILITY)

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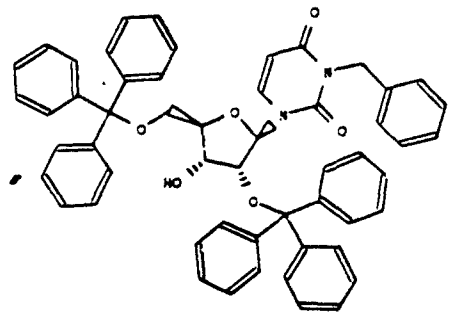
USAMRIID

Antiviral Drug Screening Program

03/26/90

TRUCTURE

CHIRAL



SUBMITTER	CTR NO	AVS NO
01141.01	KN-V-109	AVS-006443
DATE RECD	**AMT RECEIVED [mg]**	**MOL WT (au)**
12-28-89	86.00	818.979

HANDLING/STORAGE

SOLUBILITY

STABILITY

ALT NAME

N3-BENZYL-2',5'-DI-O-TRITYLURIDINE

POUND NAME

N3-BENZYL-2',5'-DI-O-TRITYLURIDINE

SCREEN INSTRUCTION

ORITY=RT>VEE>YF>KHF>PIC>JE>SF>VV>AD2>VSV

IN VIVO TOXICITY [mg/kg]

HOST	VH	RTE	LD50	MTC	LAB PR	DATE

IN VITRO SCREEN [ug/ml]

VR	VR+	ID50	CELL	MTC	TI	TI+	LAB PRT	DATE
	NOT ACT		VERO	24.7	0		SO MTT	90-03-01
	77.1		VERO	210	> 4.15		SO MTT	90-03-01
	NOT ACT		VERO	> 320	0		SO MTT	90-03-01
	NOT ACT		VERO	> 320	0		SO MTT	90-03-02
	NOT ACT		VERO	> 320	0		SO MTT	90-03-01

IN VIVO SCREEN [Dose = mg/kg]

VIR	HST	VR	VR+	DOSE	MTC	VEH	RTE	D	TOX	SP	L	PR	DATE

PLATE U9A
DRUG 6443

IN VITRO ANTIVIRAL RESULTS
MTT ASSAY

DRUG: AVS 6443
TAI: >10.57 SI: 2.72

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						plasma background					
A	0.042	0.041	0.040	0.042	0.039	0.042	0.001	0.001	0.001	0.001	0.001	0.001
		cc/vc					tox	drug 6443 experimental			cc/vc	tox
B		0.951					0.830	0.378	0.357	0.334	0.746	0.879
C		1.033					0.911	0.386	0.324	0.297	0.972	0.771
D		1.139					1.015	0.406	0.436	0.343	0.800	0.866
E		0.329					0.800	0.493	0.491	0.497	0.334	0.814
F		0.389					0.734	0.695	0.713	0.683	0.342	0.716
G		0.353					0.696	0.560	0.632	0.599	0.396	0.751
							drug 6443 colorimetric background					
H							0.059	0.044	0.040	0.039	0.040	0.040

tox=cell toxicity cc=cell control vc=virus control BOLD = highest drug conc values shown are optical densities

VIRUS	PT
CELLS	VERO
SHIPMENT NUMBER	63
STRN	ADAMES
REAGENT	0.041
VIRUS CONTROL	0.316
CELL CONTROL	0.899
DIFFERENTIAL	0.583

Satisfactory; Active; Retest

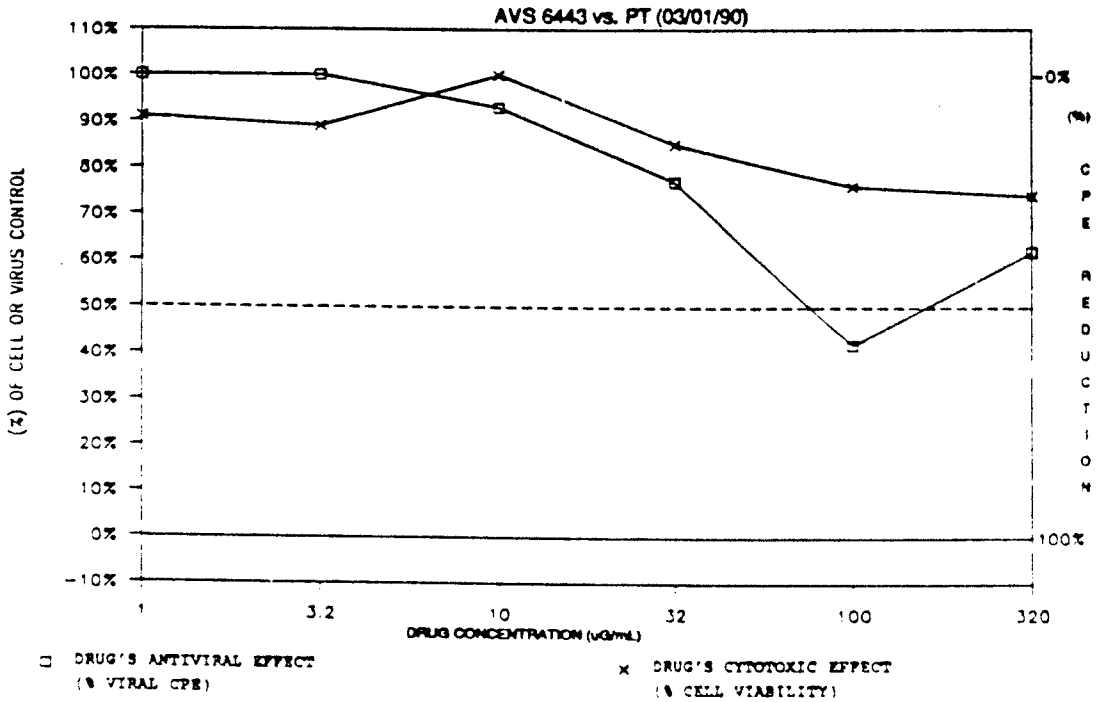
PROJECT #	5975-1
SPONSOR	USAMRIID
TEST DATE	03/01/90
DATE READ	03/09/90

DRUG 6443	25%	50%	95%
TC (uG/mL)	210.00	> 320.00	> 320.00
IC (uG/mL)	34.20	77.10	-----
ANTIVIRAL INDEX (AI)	6.15	> 4.15	-----

DRUG 6443		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		
ROW ON PLATE	CONC. (uG/mL)	MEAN O.D.	% VIRAL CPE	MEAN O.D.	% CELL VIABILITY	COLORIMETRIC CONTROL
low B	1	-.001	100%	0.815	91%	-.001
C	3.2	-.021	100%	0.801	89%	-.001
D	10	0.040	93%	0.902	100%	-.002
E	32	0.137	77%	0.767	85%	-.001
F	100	0.337	42%	0.681	76%	0.003
high G *	320	0.222	62%	0.665	74%	0.018

* highest drug concentration tested values shown are final adjusted numbers

SUMMARY GRAPH



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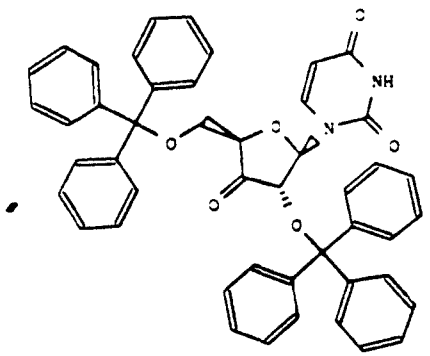
USAMRIID

Antiviral Drug Screening Program

01/26/90

STRUCTURE CHIRAL



SUBMITTER	CTR NO	AVS NO
01141.01	KN-VII-83	AVS-006444
DATE RECD	**AMT RECEIVED [mg]**	**MOL WT (g/)**
12-28-89	79.00	726.837

HANDLING/STORAGE

SOLUBILITY

STABILITY

ALT NAME

3'-DEOXY-2',5'-DI-O-TRITYL-3'-OXOURIDINE

COMPOUND NAME

3'-DEOXY-2',5'-DI-O-TRITYL-3'-OXOURIDINE

SCREEN INSTRUCTION

PRIORITY=PT>VEE>YF>KHF>RIC>JE>SF>VV>AD2>VSV

IN VIVO TOXICITY [mg/kg]

HOST	VR	RTE	LD50	MTC	LAB PR	DATE

IN VITRO SCREEN [ug/ml]

VIR	VR	VR•	CD50	CELL	MTC	TI	TI•	LAB PRT	DATE
JE			NOT ACT	VERO	51	0		SO MTT	90-03-01
PT			79.2	VERO	> 320	> 4.04		SO MTT	90-03-01
SF			NOT ACT	VERO	30	0		SO MTT	90-03-01
VEE			NOT ACT	VERO	> 320	0		SO MTT	90-03-02
YF			NOT ACT	VERO	> 320	0		SO MTT	90-03-01

IN VIVO SCREEN [Dose = mg/kg]

VIR	HST	VR	VR•	DOSE	MTC	VEH	RTE	# TOX	SP L	PR	DATE

PLATE U98
DRUG 6444

IN VITRO ANTIVIRAL RESULTS
MTT ASSAY

DRUG: AVS 6444
TAI: >24.65 SI: >4.04

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						plates background					
A	0.043	0.042	0.045	0.041	0.040	0.042	0.001	0.001	0.001	0.001	0.001	0.001
	low	cells	drug 6444 experimental			low					cells	
B	1.033	0.918	0.365	0.330	0.321	0.864					0.837	
C	0.959	0.946	0.304	0.333	0.381	0.999					0.734	
D	0.936	1.054	0.433	0.451	0.414	0.883					0.631	
E	0.811	0.295	0.382	0.411	0.490	0.810					0.339	
F	0.753	0.355	0.577	0.706	0.655	0.748					0.369	
G	0.982	0.382	0.952	0.924	0.879	0.981					0.358	
	drug 6444 colorimetric background											
H	0.041	0.043	0.042	0.039	0.039	0.039						

toxic toxicity · cells control · virus control · BOLD = highest drug conc · values shown are optical densities

VIRUS	PT		PROJECT # 5975-1
CELLS	VERO	Satisfactory; Active; Retest	SPONSOR USAMRIID
SHIPMENT NUMBER	63		TEST DATE 03/01/90
STRN	ADAMS		DATE READ 03/09/90
REAGENT	0.042		
VIRUS CONTROL	0.308		
CELL CONTROL	0.811		
DIFFERENTIAL	0.504		

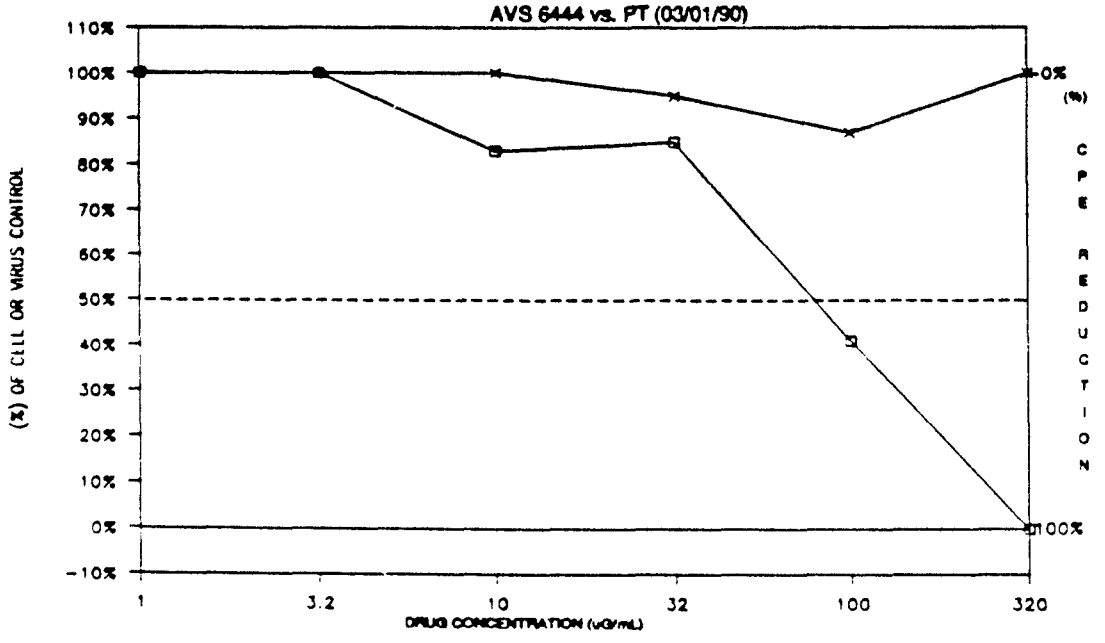
DRUG 6444	25%	50%	95%
TC (uG/mL)	> 320.00	> 320.00	> 320.00
IC (uG/mL)	41.50	79.20	278.00
ANTIVIRAL INDEX (AI)	> 7.72	> 4.04	> 1.15

DRUG 6444		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		
ROW ON PLATE	CONC. (uG/mL)	MEAN O.D.	% VIRAL CPE	MEAN O.D.	% CELL VIABILITY	COLORIMETRIC CONTROL
low B	1	-.008	100%	0.909	100%	-.003
C	3.2	-.007	100%	0.940	100%	-.003
D	10	0.086	83%	0.870	100%	-.003
E	32	0.078	85%	0.768	95%	-.000
F	100	0.295	41%	0.707	87%	0.001
high G *	320	0.570	0%	0.940	100%	-.001

* highest drug concentration tested · values shown are final adjusted numbers

SUMMARY GRAPH

AVS 6444 vs. PT (03/01/90)



□ DRUG'S ANTIVIRAL EFFECT (% VIRAL CPE)

× DRUG'S CYTOTOXIC EFFECT (% CELL VIABILITY)

PRINTED 03/16/90

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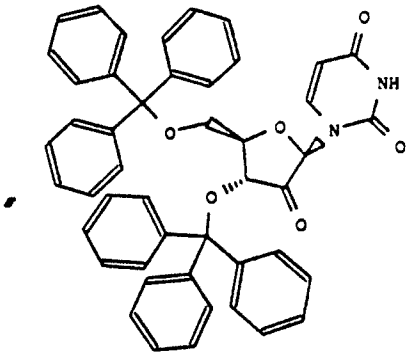
USAMRIID

Antiviral Drug Screening Program

03/26/90

STRUCTURE CHIRAL



SUBMITTER	CTR NO	AVS NO
01141.01	KN-VII-21	AVS-006445

DATE RECD	AMT RECEIVED [mg]	MOL WT (au)
12-28-89	74.00	726.837

HANDLING/STORAGE

SOLUBILITY

STABILITY

ALT NAME

2'-DEOXY-3',5'-DI-O-TRITYL-2'-OXOURIDINE

COMPOUND NAME

2'-DEOXY-3',5'-DI-O-TRITYL-2'-OXOURIDINE

SCREEN INSTRUCTION

PRIORITY=PT>VEE>YF>RHF>PIC>JE>SF>VV>AD2>VSV

IN VIVO TOXICITY [mg/kg]

HOST	VH	RTE	LD50	MTC	LAB PR	DATE

IN VITRO SCREEN [ug/ml]

VIR	VR	VR+	ID50	CELL	MTC	TI	TI+	LAB PRT	DATE
JE			NOT ACT	VERO	23.2	0		SO MTT	90-03-01
PT			22.6	VERO	49	2.92		SO MTT	90-03-01
SF			NOT ACT	VERO	43.3	0		SO MTT	90-03-01
VEE			NOT ACT	VERO	32	0		SO MTT	90-03-02
YF			18.9	VERO	48	3.45		SO MTT	90-03-01

IN VIVO SCREEN [Dose = mg/kg]

VIR	HST	VR	VR+	DOSE	MTC	VOH	RTE	D TOX	SP L	PR	DATE

PLATE U9B
DRUG 6445

IN VITRO ANTIVIRAL RESULTS
MTT ASSAY

DRUG: AVS 6445
TAI: >17.14 SI: 2.17

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						plastic background					
A	0.043	0.042	0.045	0.041	0.040	0.042	0.001	0.001	0.001	0.001	0.001	0.001
	cell/v						tox	drug 6445 experimental			cc/vc	tox
B		0.918					0.833	0.402	0.373	0.379	0.837	0.871
C		0.946					1.074	0.286	0.430	0.407	0.734	0.870
D		1.054					0.830	0.587	0.567	0.534	0.631	0.816
E		0.295					0.882	0.656	0.606	0.590	0.339	0.890
F		0.355					0.033	0.036	0.038	0.035	0.369	0.033
G		0.382					0.035	0.036	0.036	0.036	0.358	0.037
							drug 6445 colorimetric background					
H							0.038	0.044	0.043	0.040	0.039	0.039

tox=cell toxicity cc/vc=cell control vc=virus control BOLD = highest drug conc values shown are optical densities

VIRUS	PT		PROJECT # 5975-1
CELLS	VERO	Satisfactory; Active; Retest	SPONSOR USAMRIID
SHIPMENT NUMBER	63		TEST DATE 03/01/90
STRN	ADAMS		DATE READ 03/09/90
REAGENT	0.042		
VIRUS CONTROL	0.308		
CELL CONTROL	0.811		
DIFFERENTIAL	0.504		

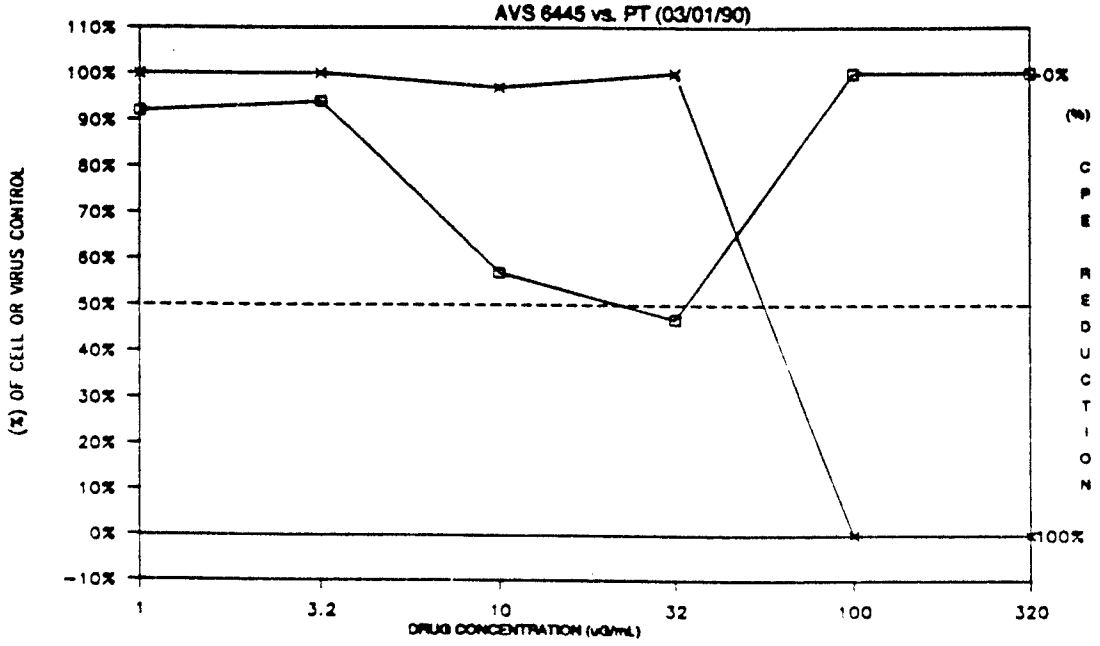
DRUG 6445	25%	50%	95%
TC (uG/mL)	49.00	66.00	96.60
IC (uG/mL)	5.74	22.60	-----
ANTIVIRAL INDEX (AI)	8.53	2.92	-----

DRUG 6445		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		
ROW ON PLATE	CONC. (uG/mL)	MEAN O.D.	% VIRAL CPE	MEAN O.D.	% CELL VIABILITY	COLORIMETRIC CONTROL
low B	1	0.038	92%	0.813	100%	-.003
C	3.2	0.028	94%	0.933	100%	-.003
D	10	0.215	57%	0.783	97%	-.002
E	32	0.267	47%	0.843	100%	0.001
F	100	-.315	100%	-.011	0%	0.002
high G *	320	-.310	100%	-.002	0%	-.004

* highest drug concentration tested values shown are final adjusted numbers

SUMMARY GRAPH

AVS 6445 vs. PT (03/01/90)



□ DRUG'S ANTIVIRAL EFFECT (% VIRAL CPE)

× DRUG'S CYTOTOXIC EFFECT (% CELL VIABILITY)

PRINTED 03/15/90

PLATE UAR | **IN VITRO ANTIVIRAL RESULTS** | **DRUG: AVS 6445**

DRUG 6445 | MTT ASSAY | TAI: >19.99 SI: 2.53

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						plastic background					
A	0.042	0.040	0.039	0.038	0.039	0.039	0.001	0.001	0.001	0.001	0.001	0.001
		cc/vc					tox	drug 6445 experimental			cc/vc	tox
B		0.847					0.912	0.290	0.356	0.317	0.926	0.943
C		1.048					0.867	0.433	0.439	0.426	0.782	0.925
D		0.922					0.767	0.426	0.441	0.474	0.882	0.834
E		0.213					0.857	0.621	0.700	0.670	0.218	0.916
F		0.253					0.034	0.033	0.034	0.034	0.176	0.042
G		0.297					0.035	0.036	0.035	0.035	0.190	0.038
							drug 6445 colorimetric background					
H							0.038	0.041	0.044	0.039	0.040	0.042

tox=cell toxicity cc=cell control vc=virus control BOLD = highest drug conc values shown are optical densities

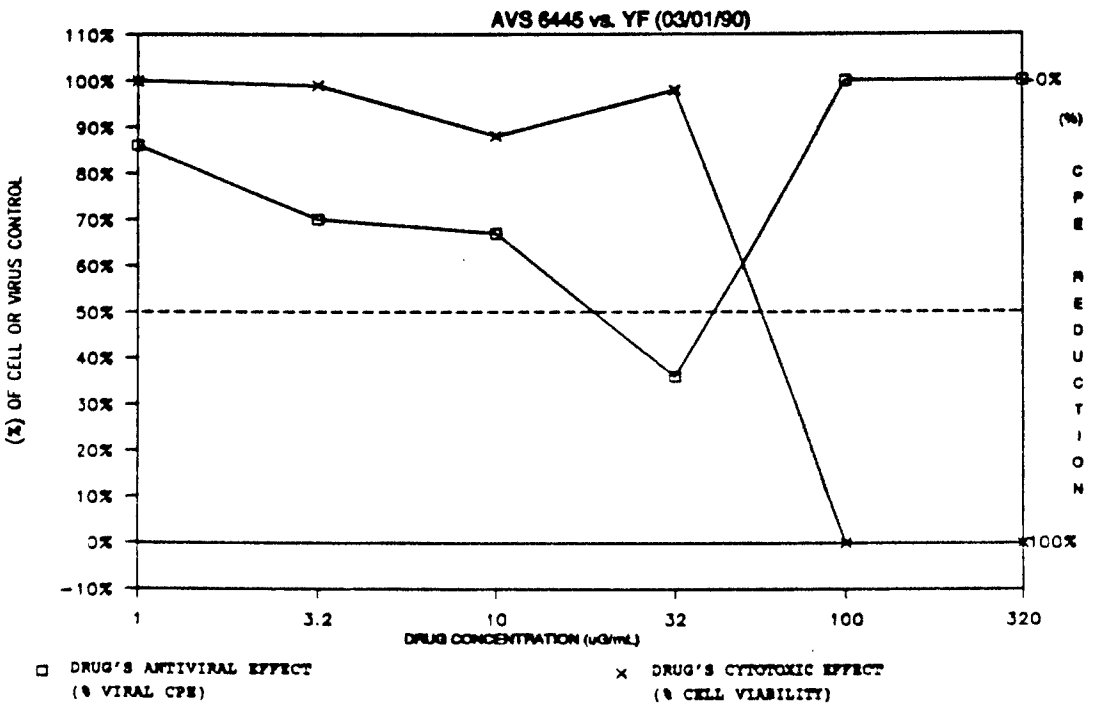
VIRUS	YF		PROJECT # 5975-1
CELLS	VERO	Satisfactory; Active; Retest	SPONSOR USAMRIID
SHIPMENT NUMBER	63		TEST DATE 03/01/90
STRN	ASIBI		DATE READ 03/09/90
REAGENT	0.040		
VIRUS CONTROL	0.185		
CELL CONTROL	0.862		
DIFFERENTIAL	0.677		

DRUG 6445	25%	50%	95%
TC (uG/mL)	48.00	65.30	96.50
IC (uG/mL)	2.22	18.90	------
ANTIVIRAL INDEX (AI)	21.56	3.45	------

DRUG 6445		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		
ROW ON PLATE	CONC. (uG/mL)	MEAN O.D.	% VIRAL CPE	MEAN O.D.	% CELL VIABILITY	COLORIMETRIC CONTROL
low B	1	0.094	86%	0.885	100%	0.003
C	3.2	0.204	70%	0.856	99%	0.001
D	10	0.224	67%	0.762	88%	-.001
E	32	0.435	36%	0.843	98%	0.004
F	100	-.193	100%	-.003	0%	0.002
high G *	320	-.187	100%	-.001	0%	-.002

* highest drug concentration tested values shown are final adjusted numbers

SUMMARY GRAPH



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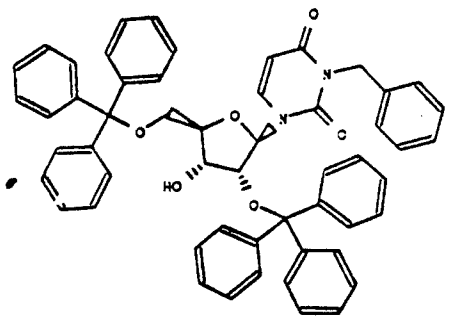
STRUCTURE CHIRAL



SUBMITTER	CTR NO	AVS NO
01141.01	KN-V-109	AVS-006443
DATE RECD	**AMT RECEIVED [mg]**	**MOL WT (au)**
12-28-89	86.00	818.979

HANDLING/STORAGE

SOLUBILITY

STABILITY

ALT NAME

N3-BENZYL-2',5'-DI-O-TRITYLURIDINE

COMPOUND NAME

N3-BENZYL-2',5'-DI-O-TRITYLURIDINE

SCREEN INSTRUCTION

PRIORITY=PT>VEE>YF>KHF>PIC>JE>SF>VV>AD2>VSV

IN VIVO TOXICITY [mg/kg]

HOST	VH	RTE	LD50	MTC	LAB PR	DATE

IN VITRO SCREEN [ug/ml]

VIR	VR	VR•	ID50	CELL	MTC	TI	TI•	LAB PRT	DATE
HIV			NOT ACT	MT2	> 100	0		SO MTT	90-03-20
JE			NOT ACT	VERO	531	0		SO MTT	90-03-22
JE			NOT ACT	VERO	24.7	0		SO MTT	90-03-01
PT			77.1	VERO	210	> 4.15		SO MTT	90-03-01
PT			NOT ACT	VERO	335	0		SO MTT	
SF			NOT ACT	VERO	441	0		SO MTT	90-03-22
SF			NOT ACT	VERO	> 320	0		SO MTT	90-03-01
VEE			NOT ACT	VERO	773	0		SO MTT	90-03-23
VEE			NOT ACT	VERO	> 320	0		SO MTT	90-03-02
VV			NOT ACT	VERO	124	0		SO MTT	90-03-23
YF			NOT ACT	VERO	427	0		SO MTT	90-03-22
YF			NOT ACT	VERO	> 320	0		SO MTT	90-03-01

IN VIVO SCREEN [Dose = mg/kg]

VIR	HST	VR	VR•	DOSE	MTC	VEH	RTE	D	TOX	SP	L	PR	DATE

PLATE UQ9 — IN VITRO ANTIVIRAL RESULTS — DRUG: AVS 6443

DRUG 6443 — MTT ASSAY — TAI: >8.74 SI: 0.00

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						plasma background					
A	0.061	0.061	0.061	0.059	0.059	0.062	0.001	0.001	0.002	0.002	0.001	0.002
	tox	cc/vc	drug 6443 experimental			tox					cc/vc	
B	1.421	1.475	0.417	0.536	0.571	1.230					1.590	
C	1.514	1.258	0.406	0.411	0.448	0.783					0.962	
D	1.327	1.605	0.658	0.571	0.499	1.230					1.198	
E	1.281	0.452	0.761	0.771	0.763	1.170					0.434	
F	1.222	0.408	0.872	0.841	0.865	1.158					0.366	
G	0.678	0.466	0.284	0.271	0.382	0.582					0.425	
	drug 6443 colorimetric background											
H	0.207	0.089	0.068	0.064	0.064	0.064						

tox=most toxicity cc=cell control vc=virus control BOLD = highest drug conc values shown are optical densities

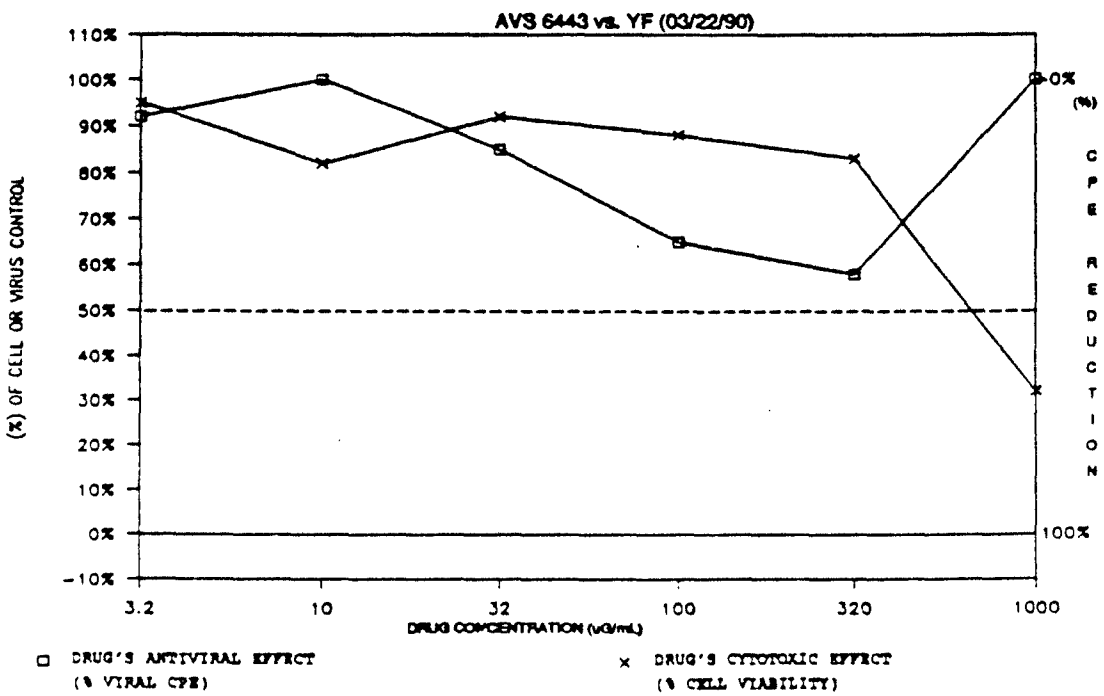
VIRUS	YF		PROJECT #	5975-1
CELLS	VERO	Satisfactory; Active; Retest	SPONSOR	USAMRIID
SHIPMENT NUMBER	63	TOXICITY RERUN	TEST DATE	03/22/90
STRN	ASIBI		DATE READ	03/30/90
REAGENT	0.061			
VIRUS CONTROL	0.365			
CELL CONTROL	1.321			
DIFFERENTIAL	0.956			

DRUG 6443	25%	50%	95%
TC (uG/mL)	427.00	760.00	> 1000.00
IC (uG/mL)	56.60	-----	-----
ANTIVIRAL INDEX (AI)	7.54	0.00	0.00

DRUG 6443		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		
ROW ON PLATE	CONC. (uG/mL)	MEAN O.D.	% VIRAL CPE	MEAN O.D.	% CELL VIABILITY	COLORIMETRIC CONTROL
low B	3.2	0.079	92%	1.261	95%	0.004
C	10	-.008	100%	1.084	82%	0.004
D	32	0.147	85%	1.214	92%	0.004
E	100	0.332	65%	1.157	88%	0.008
F	320	0.405	58%	1.101	83%	0.029
high G *	1000	-.260	100%	0.423	32%	0.147

* highest drug concentration tested — values shown are final adjusted numbers

SUMMARY GRAPH



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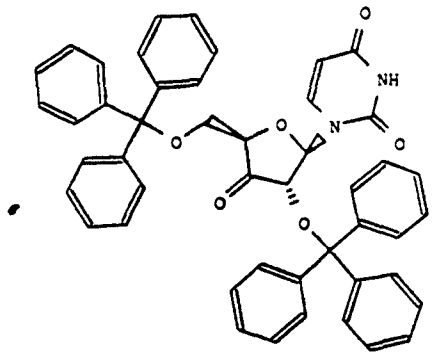


SUBMITTER	CTR NO	AVS NO
01141.01	KN-VII-83	AVS-006444

DATE RECD	AMT RECEIVED [mg]	MOL WT (au)
12-28-89	79.00	726.837

HANDLING/STORAGE

SOLUBILITY

STABILITY

ALT NAME

3'-DEOXY-2',5'-DI-O-TRITYL-3'-OXOURIDINE

COMPOUND NAME

3'-DEOXY-2',5'-DI-O-TRITYL-3'-OXOURIDINE

SCREEN INSTRUCTION

PRIORITY=PT>VEE>YF>KHF>PIC>JE>SF>VV>AD2>VSV

IN VIVO TOXICITY [mg/kg]

HOST	VH	RTE	LD50	MTC	LAB PR	DATE

IN VITRO SCREEN [ug/ml]

VIR	VR	VR+	ID50	CELL	MTC	TI	TI+	LAB PRT	DATE
HIV			NOT ACT	MT2	> 100	0		SO MTT	90-03-20
JE			NOT ACT	VERO	51	0		SO MTT	90-03-01
JE			NOT ACT	VERO	547	0		SO MTT	90-03-22
PT			79.2	VERO	> 320	> 4.04		SO MTT	90-03-01
PT			NOT ACT	VERO	257	0		SO MTT	
SF			NOT ACT	VERO	30	0		SO MTT	90-03-01
SF			NOT ACT	VERO	365	0		SO MTT	90-03-22
VEE			NOT ACT	VERO	680	0		SO MTT	90-03-23
VEE			NOT ACT	VERO	> 320	0		SO MTT	90-03-02
VV			NOT ACT	VERO	116	0		SO MTT	90-03-22
YF			29.8	VERO	410	24.55		SO MTT	90-03-22
YF			NOT ACT	VERO	> 320	0		SO MTT	90-03-01

IN VIVO SCREEN [Dose = mg/kg]

VIR	HST	VR	VR+	DOSE	MTC	VEH	RTE	D TOX	SP L	PR	DATE

PLATE UQO — **IN VITRO ANTIVIRAL RESULTS** — **DRUG: AVS 6444**

DRUG 6444 — **MTT ASSAY** — TAI: 3.21 SI: ———

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						plate background					
A	0.077	0.073	0.071	0.070	0.072	0.072	0.001	0.001	0.002	0.001	0.002	0.002
		cc/vc					tox	drug 6444 experimental			cc/vc	tox
B		1.519					1.517	0.509	0.525	0.554	1.544	1.671
C		1.478					1.483	0.458	0.481	0.478	1.484	1.577
D		1.487					1.474	0.462	0.467	0.492	1.537	1.384
E		0.607					1.542	0.621	0.651	0.640	0.589	1.615
F		0.615					1.327	0.845	0.897	0.927	0.619	1.517
G		0.626					0.697	0.474	0.515	0.524	0.613	0.680
							drug 6444 colorimetric background					
H							0.121	0.082	0.081	0.078	0.078	0.077

tox=cell toxicity cc=cell control vc=virus control BOLD = highest drug conc values shown are optical densities

VIRUS	JE		
CELLS	VERO	Satisfactory; Active; Retest	
SHIPMENT NUMBER	63	TOXICITY RERUN	
STRN	NAKAYAMA		
REAGENT	0.073		
VIRUS CONTROL	0.539		
CELL CONTROL	1.436		
DIFFERENTIAL	0.897		

PROJECT #	5975-1		
SPONSOR	USAMRIID		
TEST DATE	03/22/90		
DATE READ	03/29/90		

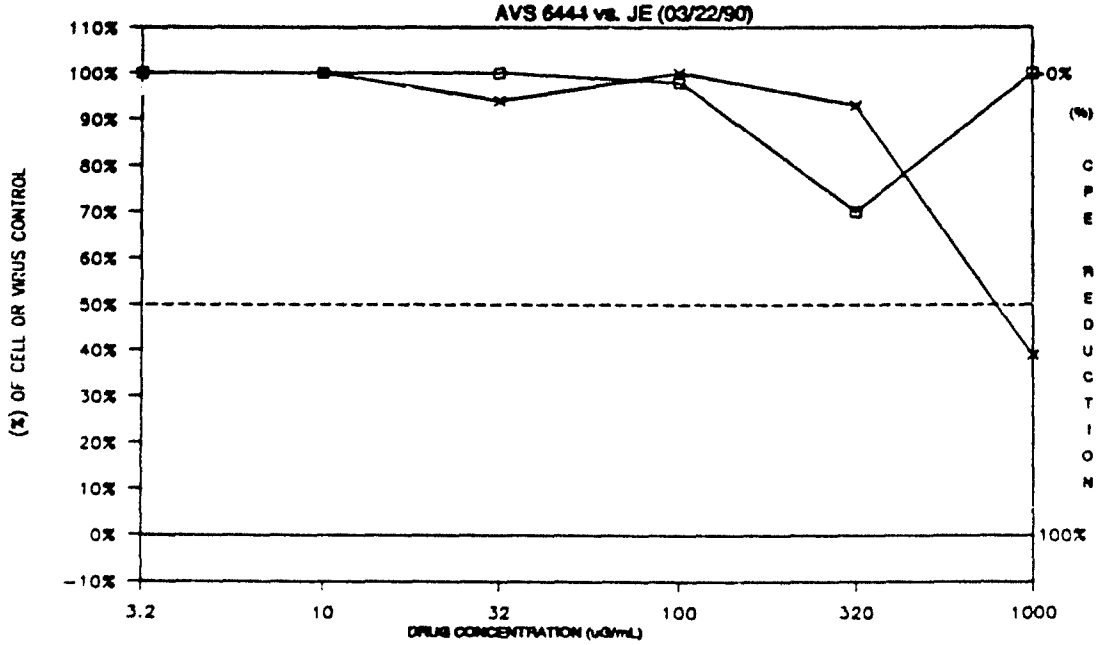
DRUG 6444	25%	50%	95%
TC (uG/mL)	547.00	861.00	> 1000.00
IC (uG/mL)	260.00	-----	-----
ANTIVIRAL INDEX (AI)	2.10	-----	-----

DRUG 6444		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		
ROW ON PLATE	CONC. (uG/mL)	MEAN O.D.	% VIRAL CPE	MEAN O.D.	% CELL VIABILITY	COLORIMETRIC CONTROL
low B	3.2	-.087	100%	1.517	100%	0.005
C	10	-.145	100%	1.452	100%	0.006
D	32	-.144	100%	1.351	94%	0.006
E	100	0.017	98%	1.497	100%	0.009
F	320	0.268	70%	1.340	93%	0.010
high G *	1000	-.156	100%	0.567	39%	0.049

* highest drug concentration tested — values shown are final adjusted numbers

SUMMARY GRAPH

AVS 6444 vs. JE (03/22/90)



□ DRUG'S ANTIVIRAL EFFECT (% VIRAL CPE)

× DRUG'S CYTOTOXIC EFFECT (% CELL VIABILITY)

PLATE URI
DRUG 6444

IN VITRO ANTIVIRAL RESULTS
MTT ASSAY

DRUG: AVS 6444
TAI: 3.44 SI: ———

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						plastic background					
A	0.054	0.055	0.054	0.051	0.051	0.053	0.002	0.002	0.001	0.001	0.001	0.001
		cc/vc					tox	drug 6444 experimental			cc/vc	tox
B		1.408					1.654	0.253	0.349	0.342	1.305	1.302
C		1.631					1.553	0.377	0.414	0.423	1.539	1.238
D		1.634					1.452	0.477	0.492	0.519	1.485	1.209
E		0.388					1.415	0.593	0.743	0.580	0.418	1.296
F		0.391					1.118	0.988	0.750	0.778	0.386	1.001
G		0.316					0.384	0.422	0.430	0.447	0.403	0.380
							drug 6444 colorimetric background					
H							0.055	0.057	0.056	0.055	0.051	0.049

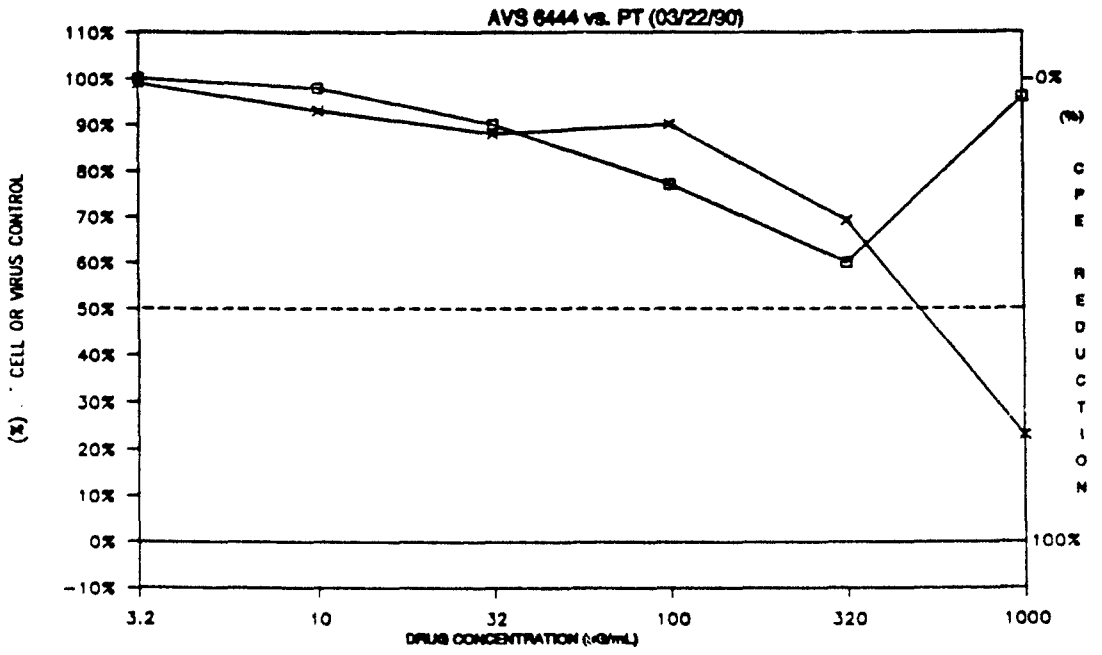
tox=cell toxicity cc=cell control vc=virus control BOLD = highest drug conc values shown are optical densities

VIRUS	PT			PROJECT #	5975-1
CELLS	VERO	Satisfactory; Active; Retest		SPONSOR	USAMRIID
SHIPMENT NUMBER	63	TOXICITY RERUN		TEST DATE	03/22/90
STRN	ADAMS6			DATE READ	03/30/90
REAGENT	0.053	DRUG 6444	25%	50%	95%
VIRUS CONTROL	0.331	TC (uG/mL)	257.00	601.00	> 1000.00
CELL CONTROL	1.447	IC (uG/mL)	115.00	-----	-----
DIFFERENTIAL	1.117	ANTIVIRAL INDEX (AI)	2.24	-----	-----

DRUG 6444		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		
ROW ON PLATE	CONC. (uG/mL)	MEAN O.D.	% VIRAL CPE	MEAN O.D.	% CELL VIABILITY	COLORIMETRIC CONTROL
low B	3.2	-.065	100%	1.429	99%	-.004
C	10	0.023	98%	1.345	93%	-.002
D	32	0.110	90%	1.276	88%	0.002
E	100	0.252	77%	1.300	90%	0.003
F	320	0.451	60%	1.003	69%	0.004
high G *	1000	0.047	96%	0.327	23%	0.002

* highest drug concentration tested values shown are final adjusted numbers

SUMMARY GRAPH



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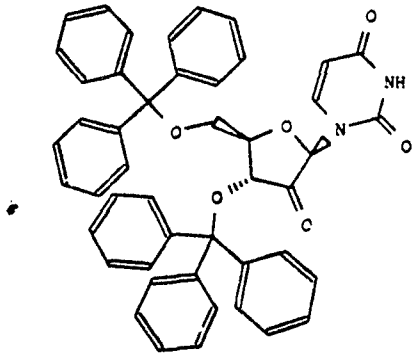


SUBMITTER	CTR NO	AVS NO
01141.01	KN-VII-21	AVS-006445

DATE RECD	AMT RECEIVED [mg]	MOL WT (au)
12-28-89	74.00	726.837

HANDLING/STORAGE

SOLUBILITY

STABILITY

ALT NAME

2'-DEOXY-3',5'-DI-O-TRITYL-2'-OXOURIDINE

COMPOUND NAME

2'-DEOXY-3',5'-DI-O-TRITYL-2'-OXOURIDINE

SCREEN INSTRUCTION

PRIORITY=PT>VEE>YF>KHF>PIC>JE>SF>VV>AD2>VSV

IN VIVO TOXICITY [mg/kg]

HOST	VH	RTE	LD50	MTC	LAB PR	DATE

IN VITRO SCREEN [ug/ml]

VIR	VR	VR•	ID50	CELL	MTC	TI	TI•	LAB PRT	DATE
HIV			NOT ACT	MT2	15.5	0		SO MTT	90-03-20
JE			NOT ACT	VERO	49	0		SO MTT	90-03-22
JE			NOT ACT	VERO	23.2	0		SO MTT	90-03-01
PT			22.6	VERO	49	2.92		SO MTT	90-03-01
PT			NOT ACT	VERO	8.87	0		SO MTT	90-03-22
SF			NOT ACT	VERO	30.4	0		SO MTT	90-01-22
SF			NOT ACT	VERO	43.3	0		SO MTT	90-03-01
VEE			NOT ACT	VERO	32	0		SO MTT	90-03-02
VEE			NOT ACT	VERO	44	0		SO MTT	90-03-23
VV			NOT ACT	VERO	4.6	0		SO MTT	90-03-22
YF			18.9	VERO	48	3.45		SO MTT	90-03-01
YF			9.06	VERO	29.6	5.83		SO MTT	90-03-22

IN VIVO SCREEN [Dose = mg/kg]

VIR	HST	VH	VR•	DOSE	MTC	VEH	RTE	D TOX	SP L	PR	DATE

PLATE UQA
DRUG 6445

IN VITRO ANTIVIRAL RESULTS
MTT ASSAY

DRUG: AVS 6445
TAI: >18.33 SI: 3.27

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						plasma background					
A	0.063	0.063	0.062	0.060	0.056	0.061	0.001	0.001	0.001	0.001	0.001	0.001
	tox	cells	drug 6445 experimental			tox					cells	
B	1.549	1.409	0.619	0.596	0.557	1.504					1.418	
C	1.442	1.368	0.740	0.805	0.674	1.607					1.392	
D	1.368	1.448	0.998	0.971	0.924	1.488					1.550	
E	1.067	0.526	0.934	0.600	0.848	1.022					0.433	
F	0.062	0.481	0.051	0.050	0.054	0.051					0.380	
G	0.066	0.494	0.066	0.061	0.059	0.065					0.400	
	drug 6445 colorimetric background											
H	0.075	0.071	0.065	0.062	0.064	0.062						

tox=cell toxicity cc=cell control vc=virus control BOLD = highest drug conc values shown are optical densities

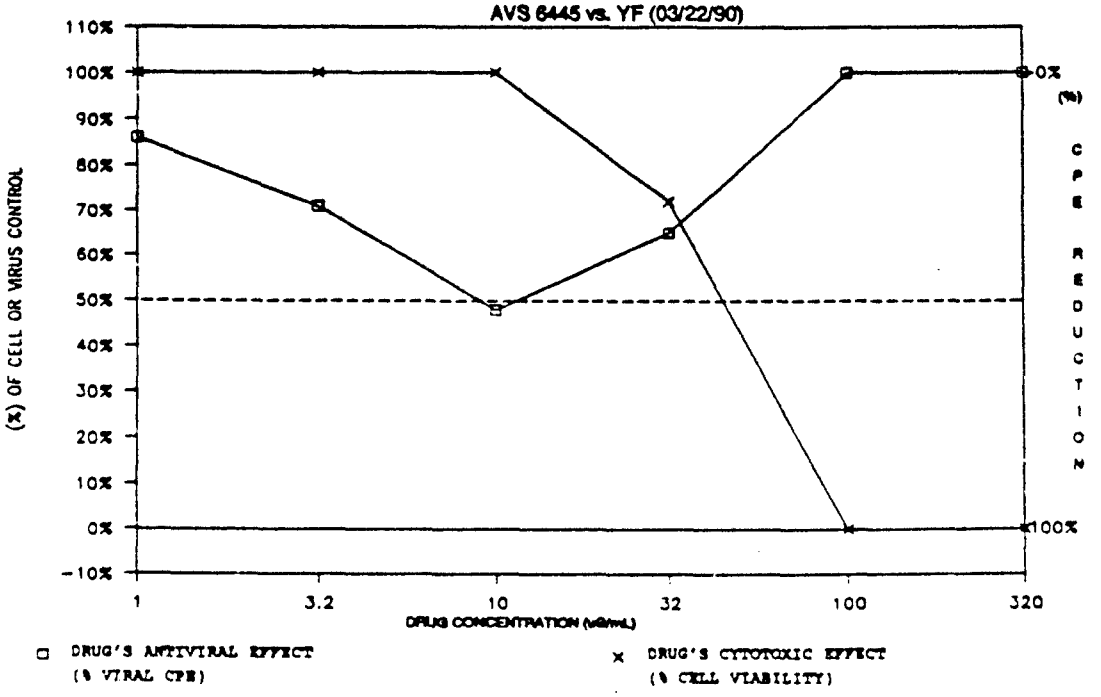
VIRUS	YF			PROJECT #	5975-1
CELLS	VERO	Satisfactory; Active; Retest		SPONSOR	USAMRIID
SHIPMENT NUMBER	63	TOXICITY RERUN		TEST DATE	03/22/90
STRN	AS IBI			DATE READ	03/30/90
REAGENT	0.061				
VIRUS CONTROL	0.392				
CELL CONTROL	1.370				
DIFFERENTIAL	0.979				

DRUG 6445	25%	50%	95%
TC (uG/mL)	29.60	52.80	95.30
IC (uG/mL)	2.35	9.06	-----
ANTIVIRAL INDEX (AI)	12.63	5.83	0.00

DRUG 6445		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		
ROW ON PLATE	CONC. (uG/mL)	MEAN O.D.	% VIRAL CPE	MEAN O.D.	% CELL VIABILITY	COLORIMETRIC CONTROL
low B	1	0.137	86%	1.465	100%	0.001
C	3.2	0.284	71%	1.461	100%	0.003
D	10	0.511	48%	1.366	100%	0.001
E	32	0.338	65%	0.980	72%	0.004
F	100	-.411	100%	-.014	0%	0.010
high G *	320	-.404	100%	-.009	0%	0.014

* highest drug concentration tested values shown are final adjusted numbers

SUMMARY GRAPH



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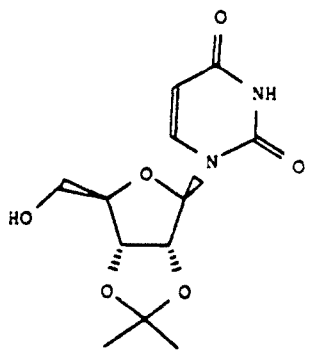
USAMRIID

Antiviral Drug Screening Program

05/18/90

TRUCTURE

CHIRAL



SUBMITTER	CTR NO	AVS NO
01141.01	KN-II-53	AVS-006449
DATE RECD	**AMT RECEIVED [mg]**	**MOL WT (au)**
12-28-89	75.00	284.271

HANDLING/STORAGE

SOLUBILITY

STABILITY

ALT NAME

2',3'-O-ISOPROPYLIDINEURIDINE

OMPOUND NAME

2',3'-O-ISOPROPYLIDINEURIDINE

SCREEN INSTRUCTION

RIORITY=PT>VEE>YF>KHF>PIC>JE>SF>VV>AD2>VSV

IN VIVO TOXICITY [mg/kg]

HOST	VH	RTE	LD50	MTC	LAB PR	DATE

IN VITRO SCREEN [ug/ml]

R	VR	VR+	ID50	CELL	MTC	TI	TI+	LAB PRT	DATE
V		NOT	ACT	MT2	> 100	0		SO MTT	90-03-20
		NOT	ACT	VERO	466	0		SO MTT	90-03-22
		NOT	ACT	VERO	> 320	0		SO MTT	90-03-01
			264	VERO	> 320	> 1.21		SO MTT	90-03-01
		NOT	ACT	VERO	363	0		SO MTT	90-03-22
		NOT	ACT	VERO	472	0		SO MTT	90-03-22
		NOT	ACT	VERO	> 320	0		SO MTT	90-03-01
E		NOT	ACT	VERO	251	0		SO MTT	90-03-02
E		NOT	ACT	VERO	320	0		SO MTT	90-03-23
		NOT	ACT	VERO	195	0		SO MTT	
		NOT	ACT	VERO	517	0		SO MTT	90-03-22
		NOT	ACT	VERO	> 320	0		SO MTT	90-03-01

IN VIVO SCREEN [Dose = mg/kg]

VIR	HST	VR	VR+	DOSE	MTC	VEH	RTE	D	TOX	SP	L	PR	DATE

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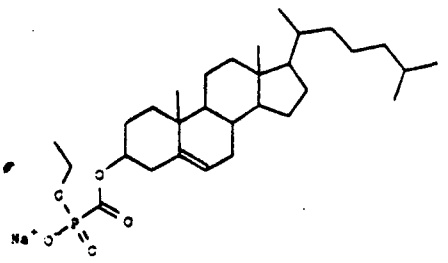
STRUCTURE



SUBMITTER	CTR NO	AVS NO
01141.01	MS-I-47	AVS-C06456
DATE RECD	**AMT RECEIVED [mg]**	**MOL WT (au)**
12-28-89	79.20	544.694

HANDLING/STORAGE

SOLUBILITY

STABILITY

ALT NAME

SODIUM ETHYL(CHOLESTERYLOXYCARBONYL)-PHOSPHONATE

COMPOUND NAME

SODIUM ETHYL(CHOLESTERYLOXYCARBONYL)-PHOSPHONATE

SCREEN INSTRUCTION

PRIORITY=PT>VEE>YF>KHF>PIC>JE>SF>VV>AD2>VSV

IN VIVO TOXICITY [mg/kg]

HOST	VH	RTE	LD50	MTC	LAB PR	DATE

IN VITRO SCREEN [ug/ml]

VIR	VR	VR•	ID50	CELL	MTC	TI	TI•	LAB	PRT	DATE
HIV			NOT ACT	MT2	49	0		SO	MTT	
JE			NOT ACT	VERO	25.6	0		SO	MTT	
JE			NOT ACT	VERO	47.4	0		SO	MTT	90-03-06
PT			NOT ACT	VERO	41.9	0		SO	MTT	90-03-06
PT			NOT ACT	VERO	43.3	0		SO	MTT	
SF			NOT ACT	VERO	50.7	0		SO	MTT	90-03-06
SF			NOT ACT	VERO	72.5	0		SO	MTT	
VEE			NOT ACT	VERO	116	0		SO	MTT	
VEE			NOT ACT	VERO	54.7	0		SO	MTT	90-03-09
VV			NOT ACT	VERO	21.8	0		SO	MTT	
YF			61	VERO	132	3.25		SO	MTT	
YF			NOT ACT	VERO	40.3	0		SO	MTT	90-03-06

IN VIVO SCREEN [Dose = mg/kg]

VIR	HST	VR	VR•	DOSE	MTC	VEH	RTE	D	TOX	SP	L	PR	DATE

PLATE UDN

DRUG 6456

IN VITRO ANTIVIRAL RESULTS
MTT ASSAY

DRUG: AVS 6456

TAI: 3.19 SI: ———

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						plates background					
A	0.059	0.057	0.063	0.055	0.063	0.054	0.001	0.001	0.002	0.002	0.001	0.002
	tox	cc/vc	drug 6456 experimental			tox					cc/vc	
B	0.936	0.768	0.225	0.228	0.213	0.841					0.941	
C	0.893	0.819	0.172	0.162	0.145	0.951					1.024	
D	0.989	0.750	0.144	0.136	0.135	1.052					0.789	
E	0.964	0.281	0.432	0.408	0.423	0.955					0.268	
F	0.174	0.271	0.053	0.051	0.052	0.077					0.265	
G	0.050	0.280	0.046	0.044	0.044	0.043					0.283	
	drug 6456 colorimetric background											
H	0.050	0.053	0.055	0.057	0.052	0.055						

tox=cell toxicity cc=cell control vc=virus control BOLD = highest drug conc values shown are optical densities

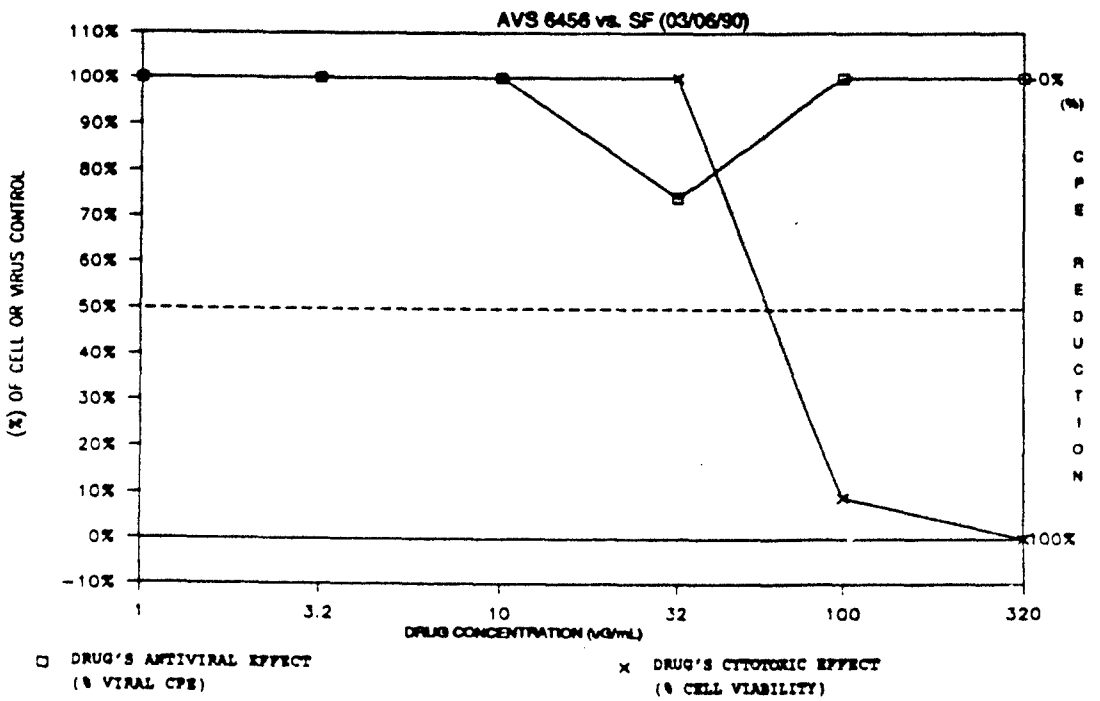
VIRUS	SF	PROJECT #	5975-1
CELLS	VERO Satisfactory; Active; Retest	SPONSOR	USAMRIID
SHIPMENT NUMBER	63	TEST DATE	03/06/90
STRN	SICILIAN	DATE READ	03/14/90
REAGENT	0.059		
VIRUS CONTROL	0.216		
CELL CONTROL	0.790		
DIFFERENTIAL	0.574		

DRUG 6456	25%	50%	95%
TC (uG/mL)	50.70	69.40	198.00
IC (uG/mL)	30.60	-----	-----
ANTIVIRAL INDEX (AI)	1.66	-----	-----

DRUG 6456		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		
ROW ON PLATE	CONC. (uG/mL)	MEAN O.D.	% VIRAL CPE	MEAN O.D.	% CELL VIABILITY	COLORIMETRIC CONTROL
low B	1	-.049	100%	0.834	100%	-.004
C	3.2	-.108	100%	0.871	100%	-.007
D	10	-.135	100%	0.963	100%	-.001
E	32	0.150	74%	0.905	100%	-.004
F	100	-.217	100%	0.073	9%	-.006
high G *	320	-.222	100%	-.004	0%	-.008

* highest drug concentration tested — values shown are final adjusted numbers

SUMMARY GRAPH

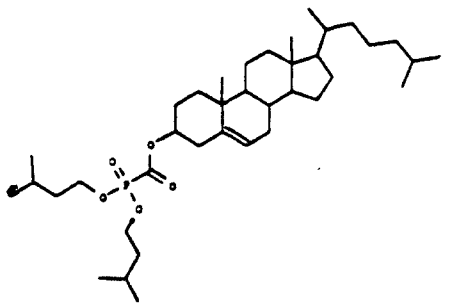


USAMRIID

Antiviral Drug Screening Program

03/18/90

STRUCTURE



SUBMITTER	CTR NO	AVS NO
01141.01	KN-I-105	AVS-006458
DATE RECD	**AMT RECEIVED [mg]**	**MOL WT (au)**
12-28-89	70.40	634.929

HANDLING/STORAGE

SOLUBILITY

STABILITY

ALT NAME
DI-ISOBUTYL(CHOLESTERYLOXYCARBONYL)-PHOSPHONATE

COMPOUND NAME
DI-ISOBUTYL(CHOLESTERYLOXYCARBONYL)-PHOSPHONATE

SCREEN INSTRUCTION

PRIORITY=PT>VEE>YF>KHF>PIC>JE>SF>VV>AD2>VSV

IN VIVO TOXICITY [mg/kg]

HOST	VN	RTE	LD50	MTC	LAB PR	DATE

IN VITRO SCREEN [ug/ml]

VIR	VR	VR•	ID50	CELL	MTC	TI	TI•	LAB PRT	DATE
HIV			NOT ACT	MT2	> 100	0		SO MTT	
JE			NOT ACT	VERO	> 320	0		SO MTT	90-03-06
JE			NOT ACT	VERO	> 1000	0		SO MTT	90-03-22
PT			NOT ACT	VERO	> 320	0		SO MTT	90-03-06
PT			NOT ACT	VERO	> 1000	0		SO MTT	90-03-22
SF			NOT ACT	VERO	> 320	0		SO MTT	90-03-06
SF			NOT ACT	VERO	> 1000	0		SO MTT	90-03-22
VEE			NOT ACT	VERO	155	0		SO MTT	90-03-09
VEE			NOT ACT	VERO	> 1000	0		SO MTT	90-03-23
VV			NOT ACT	VERO	> 320	0		SO MTT	
YF			234	VERO	> 1000	> 4.27		SO MTT	
YF			NOT ACT	VERO	> 320	0		SO MTT	90-03-06

IN VIVO SCREEN [Dose = mg/kg]

VIR	HST	VR	VR•	DOSE	MTC	VEH	RTE	D TOX	SP L	PR	DATE

PLATE UC0 | IN VITRO ANTIVIRAL RESULTS | DRUG: AVS 6458

DRUG 6458 | MTT ASSAY | TAI: >0.50 SI: ------

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						plate background					
A	0.062	0.059	0.057	0.058	0.057	0.058	0.002	0.001	0.001	0.002	0.001	0.001
	tox	cc/vc	drug 6458 experimental			tox					cc/vc	
B	1.334	1.245	0.411	0.439	0.415	1.113					1.215	
C	1.259	1.243	0.405	0.394	0.392	1.110					1.185	
D	1.298	1.283	0.365	0.422	0.412	1.110					1.211	
E	1.203	0.413	0.454	0.375	0.451	1.054					0.442	
F	1.226	0.403	0.443	0.430	0.497	1.030					0.455	
G	1.024	0.393	0.689	0.669	0.689	0.862					0.446	
	drug 6458 colorimetric background											
H	0.058	0.061	0.061	0.060	0.060	0.061						

tox=cell toxicity cc=cell control vc=virus control BOLD = highest drug conc values shown are optical densities

VIRUS	PT	PROJECT #	5975-1
CELLS	VERO Satisfactory; Active; Retest	SPONSOR	USAMRIID
SHIPMENT NUMBER	63	TEST DATE	03/06/90
STRN	ADAMS	DATE READ	02/16/90
REAGENT	0.059		
VIRUS CONTROL	0.367		
CELL CONTROL	1.172		
DIFFERENTIAL	0.805		

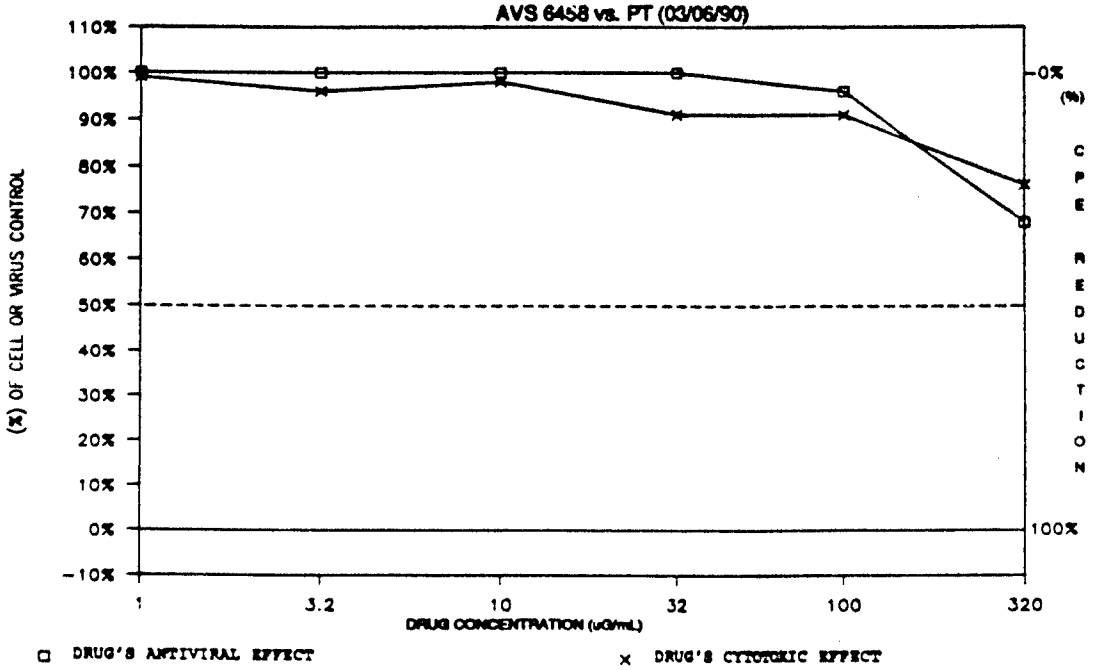
DRUG 6458	25%	50%	95%
TC (uG/mL)	> 320.00	> 320.00	> 320.00
IC (uG/mL)	239.00	-----	-----
ANTIVIRAL INDEX (AI)	> 1.34	-----	-----

DRUG 6458		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		
ROW ON PLATE	CONC. (uG/mL)	MEAN O.D.	% VIRAL CPE	MEAN O.D.	% CELL VIABILITY	COLORIMETRIC CONTROL
low B	1	-.006	100%	1.163	99%	0.002
C	3.2	-.029	100%	1.125	96%	0.001
D	10	-.027	100%	1.145	98%	0.001
E	32	-.001	100%	1.068	91%	0.002
F	100	0.029	96%	1.068	91%	0.002
high G *	320	0.257	66%	0.885	76%	0.000

* highest drug concentration tested values shown are final adjusted numbers

SUMMARY GRAPH

AVS 6458 vs. PT (03/06/90)



□ DRUG'S ANTIVIRAL EFFECT (% VIRAL CPE)

× DRUG'S CYTOTOXIC EFFECT (% CELL VIABILITY)

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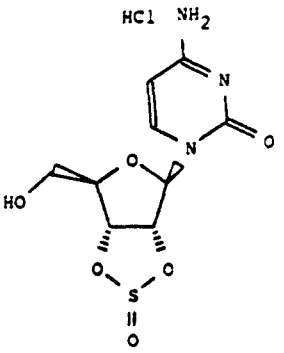
Antiviral Drug Screening Program

05/18/90

STRUCTURE CHIRAL



SUBMITTER	CTR NO	AVS NO
01141.01	KN-II-71	AVS-006462
DATE RECD	**AMT RECEIVED [mg]**	**MOL WT (au)**
12-28-89	72.40	325.729

HANDLING/STORAGE

SOLUBILITY

STABILITY

ALT NAME

2',3'-O-SULFINYLCYTIDINE HYDROCHLORIDE

COMPOUND NAME

2',3'-O-SULFINYLCYTIDINE HYDROCHLORIDE

SCREEN INSTRUCTION

PRIORITY=PT>VEE>YF>KHF>PIC>JE>SF>VV>AD2>VSV

IN VIVO TOXICITY [mg/kg]

HOST	VH	RTE	LD50	MTC	LAB PR	DATE

IN VITRO SCREEN [ug/ml]

VIR	VR'	VR+	ID50	CELL	MTC	TI	TI+	LAB	PRT	DATE
HIV			NOT ACT	MT2	.06	0		SO	MTT	
HIV			NOT ACT	MT2	< .32	0		SO	MTT	
JE			NOT ACT	VERO	22.4	0		SO	MTT	90-03-06
PT			NOT ACT	VERO	38.6	0		SO	MTT	90-03-06
SF			NOT ACT	VERO	21	0		SO	MTT	90-03-06
VEE			NOT ACT	VERO	9.73	0		SO	MTT	90-03-09
VV			1.72	VERO	16.7	14.12		SO	MTT	
VV			3.28	VERO	25.7	18.66		SO	MTT	
YF			NOT ACT	VERO	44.4	0		SO	MTT	90-03-06

IN VIVO SCREEN [Dose = mg/kg]

VIR	HST	VR	VR+	DOSE	MTC	VEH	RTE	D	TOX	SF	L	PR	DATE

PLATE 0SS | **IN VITRO ANTIVIRAL RESULTS** | **DRUG: AVS 6462**

DRUG 6462 | **MTT ASSAY** | **TAI: >32.30 SI: 7.85**

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						plasma background					
A	0.104	0.114	0.112	0.111	0.111	0.112	0.000	0.000	0.000	0.000	0.000	0.000
	cc/vc						tox	drug 6462 experimental			cc/vc	tox
B		1.542					1.492	0.362	0.278	0.427	1.506	1.619
C		1.596					1.491	0.820	0.842	0.963	1.508	1.676
D		1.651					1.650	1.412	1.560	1.551	1.524	1.770
E		0.160					1.040	0.929	0.938	0.952	0.247	1.058
F		0.248					0.573	0.511	0.523	0.524	0.174	0.542
G		0.213					0.320	0.312	0.315	0.305	0.238	0.349
							drug 6462 colorimetric background					
H							0.153	0.123	0.110	0.108	0.110	0.117

tox=cell toxicity cc=cell control vc=virus control BOLD = highest drug conc values shown are optical densities

VIRUS	VV		PROJECT # 5975-4
CELLS	VERO	Satisfactory; Active; Retest	SPONSOR USAMRIID
SHIPMENT NUMBER	63	RETEST AT 100 UG/ML	TEST DATE 03/29/90
STRN	LEDCA		DATE READ 04/04/90
REAGENT	0.111		
VIRUS CONTROL	0.103		
CELL CONTROL	1.444		
DIFFERENTIAL	1.341		

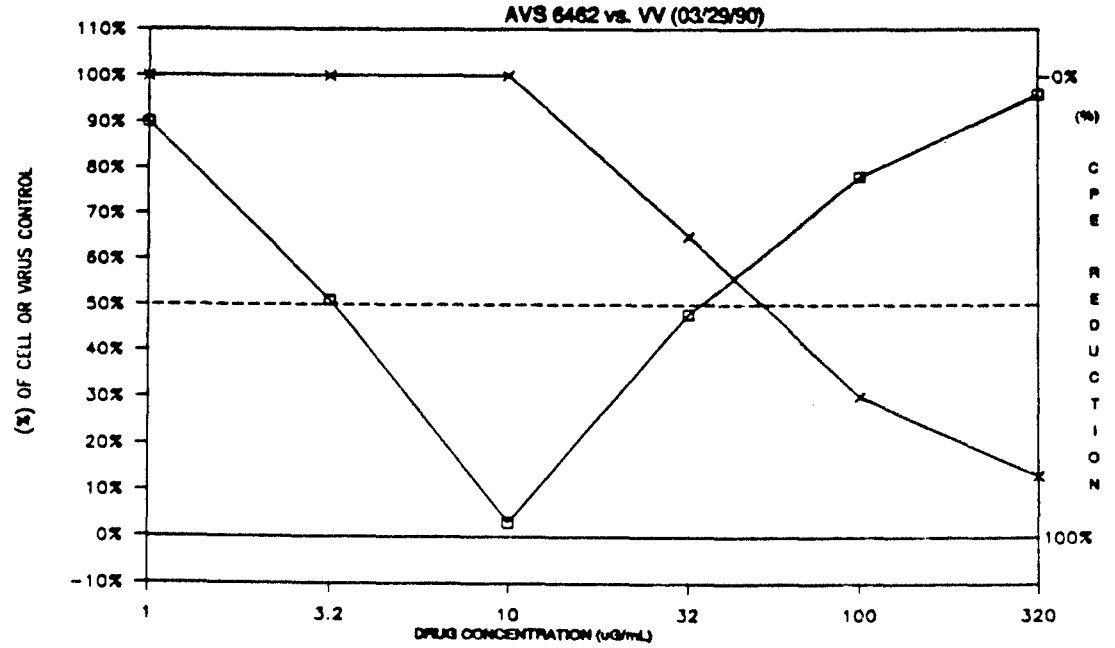
DRUG 6462	25%	50%	95%
TC (uG/mL)	25.70	61.10	> 320.00
IC (uG/mL)	1.56	3.28	9.54
ANTIVIRAL INDEX (AI)	16.46	18.66	> 33.56

DRUG 6462		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		
ROW ON PLATE	CONC. (uG/mL)	MEAN O.D.	% VIRAL CPE	MEAN O.D.	% CELL VIABILITY	COLORIMETRIC CONTROL
low B	1	0.136	90%	1.439	100%	0.006
C	3.2	0.663	51%	1.474	100%	-.001
D	10	1.297	3%	1.602	100%	-.003
E	32	0.694	48%	0.939	65%	-.001
F	100	0.294	78%	0.435	30%	0.012
high G *	320	0.055	96%	0.182	13%	0.042

* highest drug concentration tested values shown are final adjusted numbers

SUMMARY GRAPH

AVS 6462 vs. VV (03/29/90)



□ DRUG'S ANTIVIRAL EFFECT (% VIRAL CPE)

× DRUG'S CYTOTOXIC EFFECT (% CELL VIABILITY)

PLATE 0U2 — IN VITRO ANTIVIRAL RESULTS — DRUG: AVS 6462

DRUG 6462 — MTT ASSAY — TAI: 30.00 SI: 9.69

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						plastic background					
A	0.125	0.117	0.119	0.120	0.124	0.130	0.000	0.000	0.000	0.000	0.000	0.000
	test	cc/vc	drug 6462 experimental			tox					cc/vc	
B	1.284	1.387	0.125	0.155	0.151	1.443					1.322	
C	1.197	1.494	0.453	0.332	0.473	1.315					1.435	
D	1.183	1.466	1.131	1.258	1.282	1.466					1.513	
E	1.311	0.176	1.234	1.216	1.347	1.456					0.278	
F	0.415	0.176	0.359	0.399	0.430	0.446					0.187	
G	0.280	0.197	0.263	0.256	0.255	0.294					0.173	
	drug 6462 colorimetric background											
H	0.124	0.106	0.110	0.108	0.103	0.152						

test=cell toxicity cc=cell control vc=virus control BOLD = highest drug conc values shown are optical densities

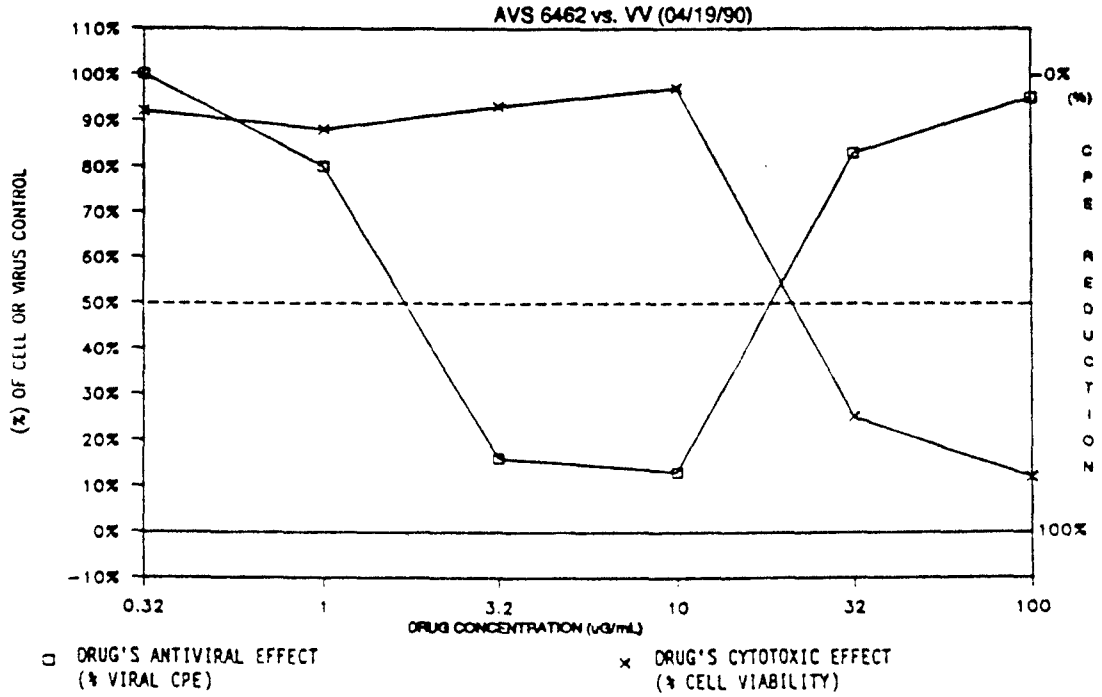
VIRUS	VV		PROJECT #	5975-4
CELLS	VERO	Satisfactory	SPONSOR	USAMRIID
SHIPMENT NUMBER	63	CONFIRMS ORIGINAL ACTIVITY	TEST DATE	04/19/90
STRN	LEDCA		DATE READ	04/25/90
REAGENT	0.123			
VIRUS CONTROL	0.075			
CELL CONTROL	1.314			
DIFFERENTIAL	1.238			

DRUG 6462	25%	50%	95%
TC (uG/mL)	16.70	24.40	> 100.00
IC (uG/mL)	1.10	1.72	-----
ANTIVIRAL INDEX (AI)	15.27	14.12	-----

DRUG 6462		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		
ROW ON PLATE	CONC. (uG/mL)	MEAN O.D.	% VIRAL CPE	MEAN O.D.	% CELL VIABILITY	COLORIMETRIC CONTROL
low B	0.32	-.084	100%	1.211	92%	0.029
C	1	0.242	80%	1.154	88%	-.020
D	3.2	1.041	16%	1.217	93%	-.015
E	10	1.081	13%	1.274	97%	-.013
F	32	0.215	83%	0.325	25%	-.017
high G *	100	0.059	95%	0.164	12%	0.001

* highest drug concentration tested values shown are final adjusted numbers

SUMMARY GRAPH



PRINTED 05/08/90

SOUTHERN RESEARCH INSTITUTE

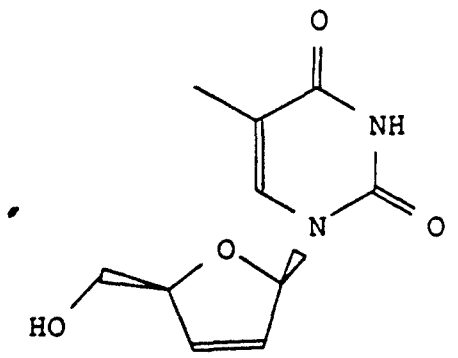
USAMRIID

Antiviral Drug Screening Program

05/18/90

STRUCTURE

CHIRAL



SUBMITTER	CTR NO	AVS NO
01141.01	KN-II-55	AVS-006466
DATE RECD	**AMT RECEIVED [mg]**	**MOL WT (au)**
12-28-89		224.218

HANDLING/STORAGE

SOLUBILITY

STABILITY

ALT NAME

2',3'-DIDEOXYTHYMIDINENE

COMPOUND NAME

2',3'-DIDEOXYTHYMIDINENE

SCREEN INSTRUCTION

PRIORITY=PT>VEE>YF>KHF>PIC>JE>SF>VV>AD2>VSV

IN VIVO TOXICITY [mg/kg]

HOST	VR	RTE	LD50	MTC	LAB PR	DATE

IN VITRO SCREEN [ug/ml]

VIR	VR	VR•	ID50	CELL	MTC	TI	TI•	LAB PRT	DATE
HIV			4.99	MT2	68.8	13.29		SO MTT	
HIVC			.32	CEM	51.5	> 222.13		SO MTT	
JE		NOT ACT		VERO	84.3	0		SO MTT	90-03-06
PT		NOT ACT		VERO	111	0		SO MTT	90-03-06
SF		NOT ACT		VERO	93.8	0		SO MTT	90-03-06
VEE		NOT ACT		VERO	232	0		SO MTT	90-03-09
YF		NOT ACT		VERO	100	0		SO MTT	90-03-06

IN VIVO SCREEN [Dose = mg/kg]

VIR	HST	VR	VR•	DOSE	MTC	VEH	RTE	D	TOX	SP	L	PR	DATE

PLATE 1HK
DRUG 6466

IN VITRO ANTIVIRAL RESULTS
MTT ASSAY

DRUG: AVS 6466
TAI: 35.67 SI: 9.78

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						plastic background					
A	0.128	0.131	0.131	0.130	0.130	0.131	0.037	0.034	0.035	0.035	0.034	0.034
	tox	cc/vc	drug 6466 experimental			tox					cc/vc	
B	1.400	1.627	0.356	0.363	0.376	1.639					1.651	
C	1.362	1.625	0.418	0.386	0.384	1.622					1.588	
D	1.367	1.657	0.627	0.570	0.580	1.712					1.666	
E	1.430	0.369	1.821	1.729	1.850	1.785					0.358	
F	1.481	0.364	1.581	1.414	1.737	1.753					0.343	
G	0.160	0.368	0.127	0.130	0.142	0.156					0.338	
	drug 6466 colorimetric background											
H	0.133	0.129	0.131	0.135	0.131	0.132						

tox=cell toxicity cc=cell control vc=virus control BOLD = highest drug conc values shown are optical densities

VIRUS	HIV3B		
CELLS	MT2	Satisfactory; Active; Retest	
SHIPMENT NUMBER	63		
STRN	2.5		
REAGENT	0.130		
VIRUS CONTROL	0.227		
CELL CONTROL	1.506		
DIFFERENTIAL	1.279		

PROJECT #	6520-2		
SPONSOR	USAMRIID		
TEST DATE	04/04/90		
DATE READ	04/12/90		

DRUG 6466	25%	50%	95%
TC (uG/mL)	48.80	66.40	97.90
IC (uG/mL)	3.53	4.99	9.33
ANTIVIRAL INDEX (AI)	13.84	13.29	10.49

DRUG 6466		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		
ROW ON PLATE	CONC. (uG/mL)	MEAN O.D.	% RED. IN VIRAL CPE	MEAN O.D.	% CELL VIABILITY	COLORIMETRIC CONTROL
low B	0.32	0.006	0%	1.387	92%	0.002
C	1	0.038	3%	1.361	90%	0.001
D	3.2	0.231	18%	1.404	93%	0.005
E	10	1.442	100%	1.476	98%	0.001
F	32	1.222	96%	1.488	99%	-.001
high G *	100	-.227	0%	0.025	2%	0.003

* highest drug concentration tested values shown are final adjusted numbers

SUMMARY GRAPH

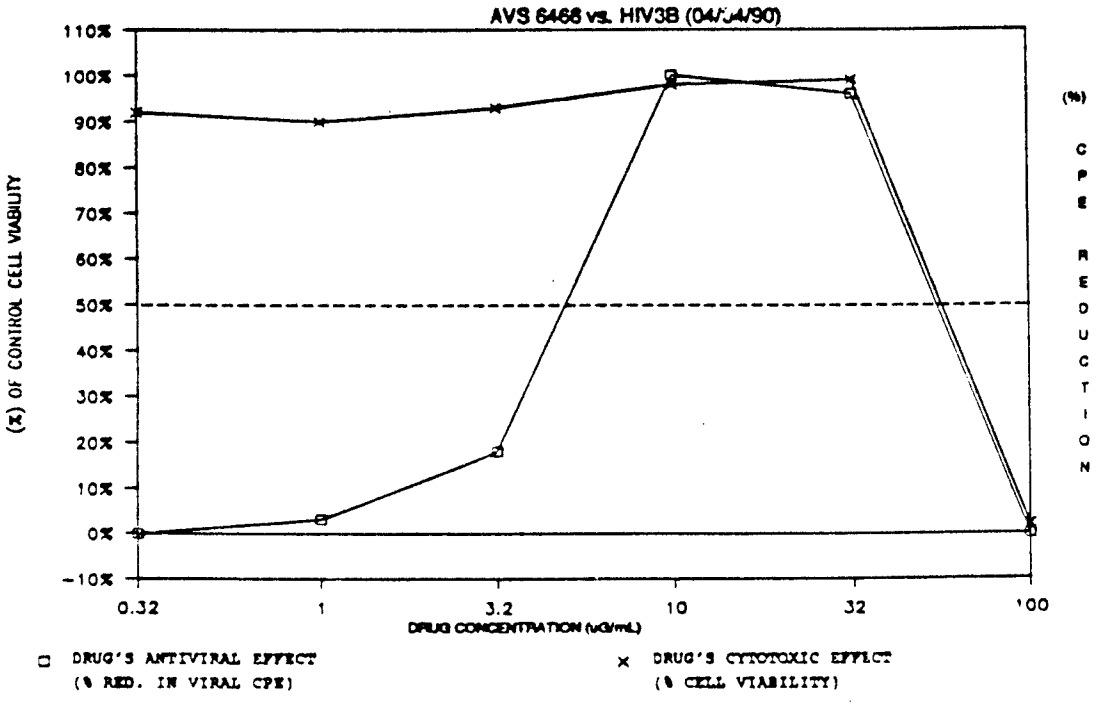


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PLATE 1KA
DRUG 6466

IN VITRO ANTIVIRAL RESULTS
MTT ASSAY

DRUG: AVS 6466
TAI: >85.47 SI: >161.06

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						plasma background					
A	0.118	0.109	0.116	0.115	0.112	0.114	0.034	0.034	0.034	0.034	0.034	0.033
		cc/vc					tox	drug 6466 experimental			cc/vc	tox
B		1.089					1.190	1.183	1.176	1.067	1.233	1.133
C		1.051					1.137	1.101	1.193	1.236	1.212	1.245
D		0.917					1.061	1.207	1.204	1.234	1.205	1.323
E		0.478					1.197	1.195	1.334	1.246	0.512	1.477
F		0.469					1.629	1.371	1.380	1.360	0.576	1.578
G		0.506					0.302	0.174	0.174	0.164	0.566	0.248
							drug 6466 colorimetric background					
H							0.144	0.137	0.135	0.126	0.121	0.132

tox=cell toxicity cc=cell control vc=virus control BOLD = highest drug conc values shown are optical densities

VIRUS	HIVCRF	PROJECT #	6520-2
CELLS	CEM	SPONSOR	USAMRIID
SHIPMENT NUMBER	64	TEST DATE	04/26/90
STRN	RF2	DATE READ	05/03/90
REAGENT	0.114		
VIRUS CONTROL	0.404		
CELL CONTROL	1.004		
DIFFERENTIAL	0.600		

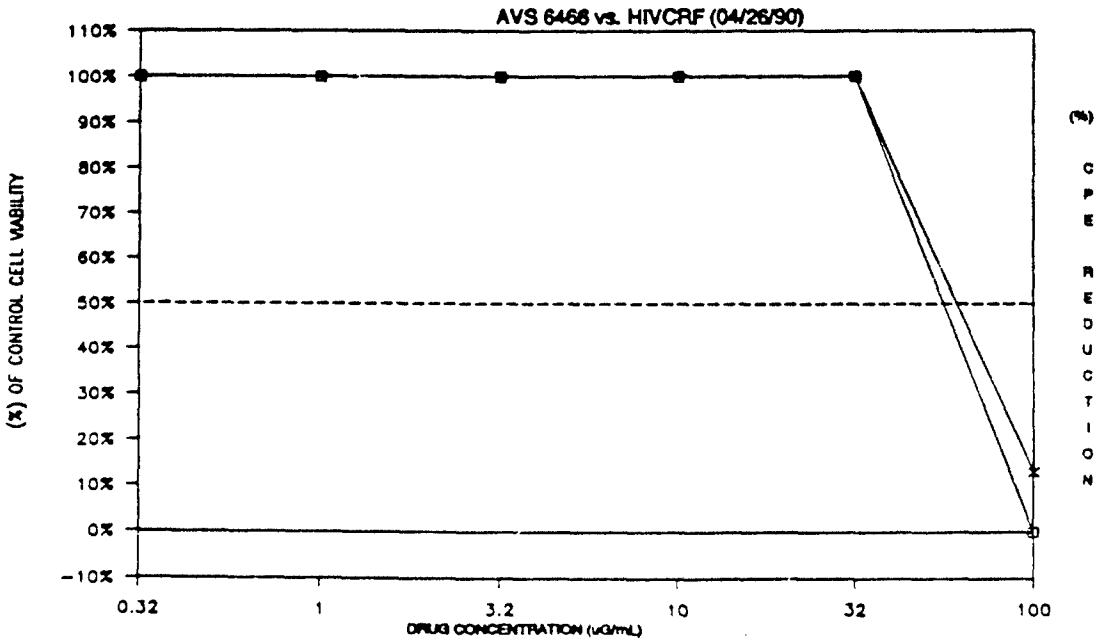
Satisfactory; Active; Retest
Low MOI

DRUG 6466	25%	50%	95%
TC (uG/mL)	51.50	71.10	> 100.00
IC (uG/mL)	< 0.32	< 0.32	< 0.32
ANTIVIRAL INDEX (AI)	> 161.06	> 222.13	> 312.50

DRUG 6466		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		
ROW ON PLATE	CONC. (uG/mL)	MEAN O.D.	% RED. IN CPE	MEAN O.D.	% CELL VIABILITY	COLORIMETRIC CONTROL
low B	0.32	0.606	100%	1.030	100%	0.018
C	1	0.652	100%	1.070	100%	0.007
D	3.2	0.685	100%	1.066	100%	0.012
E	10	0.720	100%	1.202	100%	0.021
F	32	0.830	100%	1.467	100%	0.023
high G *	100	-.377	0%	0.131	13%	0.030

* highest drug concentration tested — values shown are final adjusted numbers

SUMMARY GRAPH



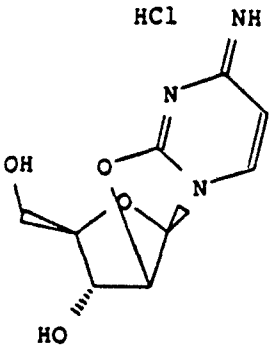
USAMRIID

Antiviral Drug Screening Program

05/18/90

STRUCTURE

CHIRAL



SUBMITTER	CTR NO	AVS NO
01141.01	KN-II-95	AVS-006467
DATE RECD	**AMT RECEIVED [mg]**	**MOL WT (au)**
12-28-89	72.60	261.667

HANDLING/STORAGE

SOLUBILITY

STABILITY

ALT NAME

2',O2-ANHYDROCYTIDINE HYDROCHLORIDE

COMPOUND NAME

2',O2-ANHYDROCYTIDINE HYDROCHLORIDE

SCREEN INSTRUCTION

PRIORITY=PT>VEE>YF>KHF>PIC>JE>SF>VV>AD2>VSV

IN VIVO TOXICITY [mg/kg]

HOST	VH	RTE	LD50	MTC	LAB PR	DATE

IN VITRO SCREEN [ug/ml]

VIR	VR	VR•	ID50	CELL	MTC	TI	TI•	LAB PRT	DATE
HIV			NOT ACT	MT2	.04	0		SO MTT	
HIV			NOT ACT	MT2	< .32	0		SO MTT	
JE			NOT ACT	VERO	.71	0		SO MTT	90-03-22
JE			NOT ACT	VERO	1.8	0		SO MTT	90-03-06
PT			NOT ACT	VERO	.48	0		SO MTT	90-03-22
PT			NOT ACT	VERO	4.99	0		SO MTT	90-03-06
SF			NOT ACT	VERO	.58	0		SO MTT	90-03-22
SF			NOT ACT	VERO	2.4	0		SO MTT	90-03-06
VEE			NOT ACT	VERO	1	0		SO MTT	90-03-09
VEE			NOT ACT	VERO	.5	0		SO MTT	90-03-23
VV			.18	VERO	.82	10.53		SO MTT	
YF			NOT ACT	VERO	.52	0		SO MTT	90-03-22
YF			NOT ACT	VERO	1.96	0		SO MTT	90-03-06

IN VIVO SCREEN [Dose = mg/kg]

VIR	HST	VR	VR•	DOSE	MTC	VEH	RTE	D TOX	SP L	PR	DATE

PLATE 0U4 | IN VITRO ANTIVIRAL RESULTS | DRUG: AVS 6467

DRUG 6467 | MTT ASSAY | TAI: 23.24 SI: 4.65

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						plastic background					
A	0.105	0.097	0.123	0.114	0.109	0.119	0.000	0.000	0.000	0.000	0.000	0.000
		co/vc					tox	drug 6467 experimental			co/vc	tox
B		1.314					1.488	0.153	0.166	0.134	1.321	1.330
C		1.339					1.510	0.179	0.148	0.205	1.470	1.424
D		1.312					1.553	0.258	0.206	0.325	1.410	1.427
E		0.182					1.415	1.153	1.398	1.302	0.160	1.541
F		0.180					1.058	0.847	0.883	0.733	0.173	0.825
G		0.174					0.450	0.426	0.446	0.427	0.142	0.400
							drug 6467 colorimetric background					
H							0.107	0.110	0.105	0.108	0.114	0.117

tox=cell toxicity co=cell control vc=virus control BOLD = highest drug conc values shown are optical densities

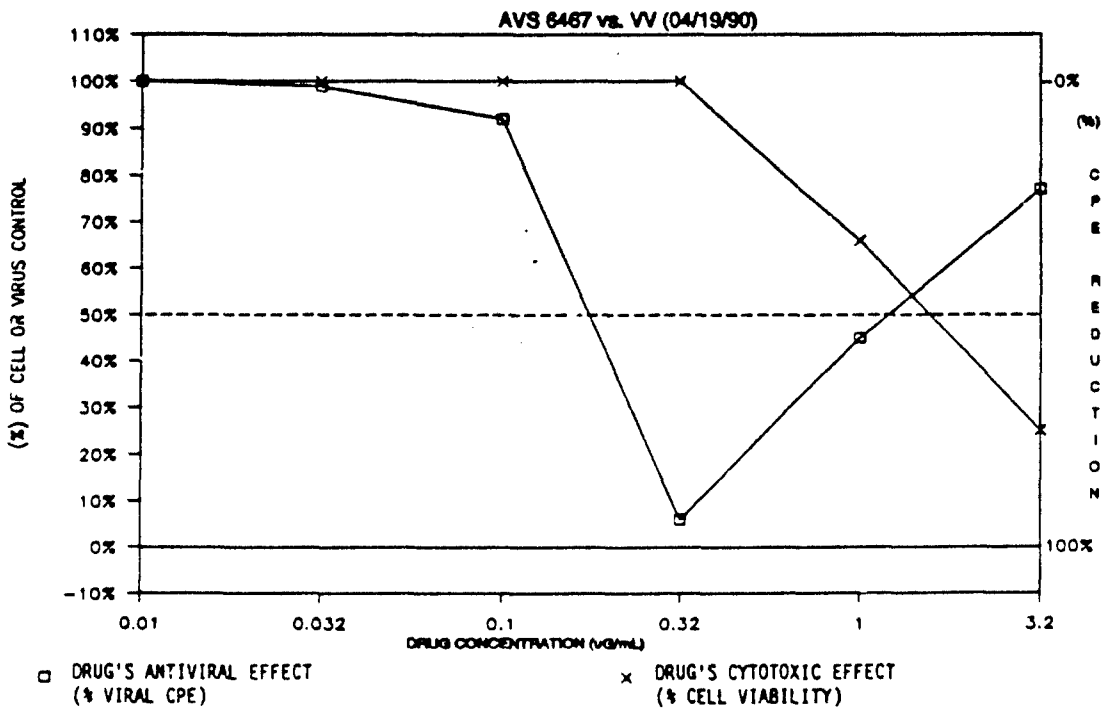
VIRUS	VV		PROJECT # 5975-4
CELLS	VERO	Satisfactory; Active; Retest	SPONSOR USAMRIID
SHIPMENT NUMBER	63	RETEST AT 3.2 UG/ML	TEST DATE 04/19/90
STRN	LEDCA		DATE READ 04/25/90
REAGENT	0.111		
VIRUS CONTROL	0.057		
CELL CONTROL	1.250		
DIFFERENTIAL	1.193		

DRUG 6467	25%	50%	95%
TC (uG/mL)	0.82	1.86	> 3.20
IC (uG/mL)	0.13	0.18	------
ANTIVIRAL INDEX (AI)	6.52	10.53	------

DRUG 6467		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		
ROW ON PLATE	CONC. (uG/mL)	MEAN O.D.	% VIRAL CPE	MEAN O.D.	% CELL VIABILITY	COLORIMETRIC CONTROL
low B	0.01	-.023	100%	1.282	100%	0.006
C	0.032	0.006	99%	1.353	100%	0.003
D	0.1	0.098	92%	1.382	100%	-.003
E	0.32	1.122	6%	1.373	100%	-.006
F	1	0.654	45%	0.831	66%	-.001
high G *	3.2	0.269	77%	0.318	25%	-.004

* highest drug concentration tested values shown are final adjusted numbers

SUMMARY GRAPH



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